PROTOCOL AMENDMENT

PRODUCT NAME/NUMBER:	DARE-VVA1 (Intravaginal Tamoxifen)
PROTOCOL NUMBER:	DARE-VVA-001
IND NUMBER:	n/a
NCT NUMBER:	n/a
DEVELOPMENT PHASE:	1/2
PROTOCOL TITLE:	Phase 1/2 Study of Intravaginal Tamoxifen (DARE-VVA1): Randomized, Double-blind, Placebo-controlled Study of Safety, Pharmacokinetics and Pharmacodynamics in Postmenopausal Participants with Moderate to Severe Vulvar and Vaginal Atrophy
PROTOCOL DATE:	Version 1.0, 29-Jun-2021
AMENDMENT 1 DATE:	Version 2.0, 15-Mar-2022
AMENDMENT 2 DATE:	Version 3.0, 04-Apr-2022
SPONSORED BY:	Daré Bioscience Australia Pty LTD Level 19 HWT Tower, 40 City Road Southbank, VIC 3006 Australia
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1. APPROVAL SIGNATURES

PROTOCOL NUMBER:	DARE-VVA1-001
PROTOCOL TITLE:	Phase 1/2 Study of Intravaginal Tamoxifen (DARE-VVA1): Randomized, Double-blind, Placebo-controlled Study of Safety, Pharmacokinetics and Pharmacodynamics in Postmenopausal Participants with Moderate to Severe Vulvar and Vaginal Atrophy
AMENDMENT 1 DATE:	Version 2.0, 15-Mar-2022
AMENDMENT 2 DATE:	Version 3.0, 04-Apr-2022

I, the undersigned, have read this protocol and confirm that to the best of my knowledge it accurately describes the planned conduct of the study.

SIGNATURE **DATE:**

Christine Mauck, MD, MPH
Medical Director
Daré Bioscience, Inc.

David Friend, PhD
Chief Scientific Officer
Daré Bioscience, Inc.

2. PROTOCOL SUMMARY

2.1. Synopsis

PRODUCT NAME/NUMBER	Tamoxifen vaginal insert / DARE-VVA1: 1, 5, 10, 20 mg
PROTOCOL NUMBER	DARE-VVA-001
DEVELOPMENT PHASE	Phase 1/2
PROTOCOL TITLE	Phase 1/2 Study of Intravaginal Tamoxifen (DARE-VVA1): Randomized, Double-blind, Placebo-controlled Study of Safety, Pharmacokinetics and Pharmacodynamics in Postmenopausal Participants with Moderate to Severe Vulvar and Vaginal Atrophy
INDICATION	Moderate to severe vulvar and vaginal atrophy (VVA)
OBJECTIVES	Primary: • To evaluate the safety and tolerability of DARE-VVA1 by intravaginal administration • To determine the plasma pharmacokinetics (PK) of DARE-VVA1 after intravaginal application Secondary: • To evaluate preliminary efficacy and pharmacodynamics (PD) of DARE-VVA1 in terms of most bothersome symptom, dyspareunia, and changes in vaginal cytology and pH Exploratory: • To evaluate the impact of DARE-VVA1 on quality of life using a menopause-specific instrument • To assess the usability and acceptability of DARE-VVA1
RATIONALE	The use of estrogen-containing products for the treatment of VVA is contraindicated in women with hormone receptor-positive (HR+) breast cancer due to their capacity to promote tumor growth. There remains a large unmet need for a novel nonhormonal VVA treatment for this subset of cancer patients and survivors, and other women who require or prefer a treatment option that does not contain estrogen. An exploratory study of intravaginal tamoxifen has demonstrated the potential for this selective estrogen receptor modulator (SERM), which acts as an estrogen receptor agonist in the vagina and as an antagonist in breast tissue, to improve VVA symptoms. The present study will evaluate different doses of DARE-VVA1, a tamoxifen vaginal insert, in postmenopausal women with VVA, including women with a history of breast cancer, to evaluate safety and tolerability, PK, initial responses to treatment, and PD.
STUDY DESIGN	This is a randomized, multi-center, double-blind, parallel-arm, placebo-controlled, dose-ranging study to evaluate the safety, tolerability, PK, and PD of DARE-VVA1, a novel intravaginal tamoxifen product. The investigational product (IP) will be evaluated at 4 dose levels (1 mg, 5 mg, 10 mg, and 20 mg) and compared to a placebo vaginal insert. The IP will be administered intravaginally for 56 days according to the following treatment schedule: once daily for 2 weeks then twice a week for 6 weeks. Approximately 40 postmenopausal women with VVA will be enrolled, 20 who have undergone hysterectomy and 20 who have not. After signing informed consent, eligible

<table>
<tr><td></td><td>participants will be randomly allocated as follows: the 20 hysterectomized women will be allocated to 1 of the 5 treatment groups, and the 20 non-hysterectomized women will be randomly allocated to one of the same 5 treatment groups, such that each treatment group ends up with 4 hysterectomized women and 4 non-hysterectomized women, for a total of 8 women. In each treatment group, participants will have serial blood sampling for PK analysis and undergo safety evaluations and preliminary assessments of effectiveness.

Following the completion of treatment, participants will attend a follow-up visit on Day 63.</td></tr>
<tr><td>PLANNED NUMBER OF PARTICIPANTS</td><td>A sufficient number of participants will be screened to randomize 40 participants (8 participants per group) to the following planned treatment groups:
<table>
<tr><th>Dose Level</th><th>Treatment</th><th>Number of Participants</th></tr>
<tr><td>Placebo</td><td>One placebo insert</td><td>N=8</td></tr>
<tr><td>1 mg</td><td>One DARE-VVA1 1 mg insert</td><td>N=8</td></tr>
<tr><td>5 mg</td><td>One DARE-VVA1 5 mg insert</td><td>N=8</td></tr>
<tr><td>10 mg</td><td>One DARE-VVA1 10 mg insert</td><td>N=8</td></tr>
<tr><td>20 mg</td><td>One DARE-VVA1 20 mg insert</td><td>N=8</td></tr>
</table></td></tr>
<tr><td>STUDY ENTRY CRITERIA</td><td>This study will enroll healthy postmenopausal females with moderate to severe VVA.

Participants must meet all inclusion criteria to be eligible for enrollment into the study. Participants will not be eligible for entry into this study if they meet any of the exclusion criteria and will be discontinued at the discretion of the investigator in consultation with the medical monitor if they develop any of the exclusion criteria during the study.

<u>Inclusion criteria</u>:

1. Women aged 40-75 (inclusive).
2. Postmenopausal women with a body mass index between 18 and 38 kg/m^2, inclusive.
3. Postmenopausal, defined as:
a. For non-hysterectomized women, 12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhea with serum follicle-stimulating hormone (FSH) levels > 40 mIU/mL or 6 weeks postsurgical bilateral oophorectomy.
b. For hysterectomized women, serum follicle-stimulating hormone (FSH) levels > 40 mIU/mL or 6 weeks postsurgical bilateral oophorectomy.
4. Have moderate to severe VVA as determined by self-assessment of the following symptoms: vaginal dryness, vaginal and/or vulvar irritation/itching, dysuria, vaginal pain with sexual activity (dyspareunia) (all self-assessed as none, mild, moderate, or severe), or vaginal bleeding associated with sexual activity (self-assessed as presence versus absence). To be eligible, at least 1 of the first 4 symptoms must be reported as moderate or severe, or vaginal bleeding associated with sexual activity must be present.
5. Women who currently have vaginal intercourse or other sexual activity (masturbation, etc.) at least once a month (with or without a partner), or who had intercourse or other sexual activity at least once a month in the past, but later decreased sexual activity due to excessive pain or vaginal dryness. Participants must be willing to engage in vaginal intercourse or other sexual activity (masturbation, etc.) at least 1 time between Days 49-56 of the clinical study.</td></tr>
</table>

	6. Participants, upon pelvic examination with speculum examination, must have a normal-appearing vulva other than atrophic changes and normal-appearing vagina (without erosions, ulcerations, scarring, or evidence of dermatoses) other than atrophic changes (loss of rugae, mucosal pallor, mucosal dryness, mucosal petechiae). Women without a cervix must have a normal-appearing vaginal cuff. 7. Women who have not undergone hysterectomy must have: a. No prior history of endometrial ablation. b. Endometrial thickness ≤ 4 mm on transvaginal ultrasound. 8. Women with a cervix must: a. Have a normal-appearing cervix other than atrophic changes (i.e., cervical stenosis and/or flushness with the vaginal wall). b. Be current on all recommended screening and management requirements for cervical cancer. 9. Vaginal cellular cytology with ≤ 5% superficial cells. 10. Vaginal pH > 5 at Screening Visit. 11. Normal mammogram report within 2 years of screening. 12. Normal manual breast examination by investigator at baseline. 13. Baseline hematology, clinical chemistry, urinalysis, coagulation, and viral serologies for human immunodeficiency virus (HIV), hepatitis C virus (HCV), and hepatitis B surface antigen (HBsAg) all within normal limits OR accepted by the investigator and medical monitor as not clinically significant. 14. Normal 12-lead electrocardiogram (ECG). 15. Able to read, understand, and provide written informed consent and applicable data protection authorization after the nature of the study has been fully explained, and must be willing to comply with all study requirements. 16. Willing and able to correctly and independently complete all study procedures. <u>Exclusion criteria</u>: 1. A history of or physical examination finding for any significant cardiovascular, renal, pulmonary, neurological and hepatic diseases preventing compliance with this study. 2. A medical history of or use of anticoagulant drugs to treat or prevent coagulopathies, thrombophilia or thromboembolic disease (deep vein thrombosis, pulmonary or systemic embolism, stroke, or transient ischemic attack). 3. Uncontrolled hypertension (either systolic > 180 mmHg or diastolic > 105 mmHg), treatment with Class 1 antiarrhythmics or digitalis, history of congestive heart failure (New York Heart Association [NYHA] > Class I), or myocardial infarction within 12 months. 4. Women with a cervix cannot have had an abnormal cervical screening test within 2 years of screening. Participants can have atypical squamous cells of undetermined significance if human papilloma virus-negative. 5. Women who have not undergone hysterectomy cannot have a history of or current endometrial pathology: hyperplasia, carcinoma and/or polyp (prior history of a benign endometrial polyp with no current evidence of polyp is acceptable).

	6. A medical history of breast cancer within 5 years of screening. Participants with a history of breast cancer more than 5 years prior to screening are considered eligible if their disease was node-negative, nonmetastatic, and if all treatment with aromatase inhibitors (AIs) or SERMs was completed at least 6 months prior to screening. 7. A medical history of malignant melanoma. 8. Any cancer (except nonmelanomatous skin cancer) diagnosed less than 5 years prior to the Screening Visit. 9. A medical history of undiagnosed vaginal bleeding. 10. A known or suspected estrogen-dependent neoplasia. 11. Previous radiation treatment to the pelvis. 12. Women who have previously reported an unsatisfactory outcome from a vaginal hormone therapy for VVA. 13. Known hypersensitivity to any ingredients in DARE-VVA1. 14. Use of vaginal hormonal products (rings, creams, gels, tablets, capsules) within 4 weeks prior to Day 1. 15. Use of transdermal estrogen products within 4 weeks prior to Day 1. 16. Use of oral estrogen therapy within 8 weeks prior to Day 1. 17. Use of estrogen-alone injectable drug therapy within 12 weeks prior to Day 1. 18. Administration of estrogen pellet therapy within 6 months prior to Day 1. 19. Use of thyroid hormone replacement therapy unless the participant is on a stable dose for > 6 months, and participant is euthyroid based on a normal, sensitive immunoassay for thyroid-stimulating hormone (TSH). 20. Use of SERMs or AIs within 6 months prior to screening. 21. Use of anabolic or other steroids (including hormonal creams such as testosterone) within 4 weeks prior to Day 1. 22. Use of corticosteroids, > 5 mg/day prednisone or equivalent, for more than 4 weeks within 4 weeks prior to Day 1. 23. Participants with any self-reported active sexually transmitted disease and/or evidence of infection (including bacterial vaginosis) on vaginal examination by the investigator. 24. Participants with a urinary tract infection during screening as assessed by urine dipstick test with abnormal test findings (any positive result for leukocytes AND any positive result for nitrites). 25. Women who have not undergone hysterectomy cannot have clinically significant uterine fibroids. 26. Evidence of current alcohol or drug abuse in the past 60 days, including a positive result from the urine drugs of abuse or alcohol screen, or history of drug or alcohol dependence in the last 2 years, as assessed by the investigator. Alcohol abuse is defined as greater than 14 standard units/week for females, and drug abuse is defined as known psychiatric or substance abuse disorder that would interfere with participation with the requirements of this study, including current use of any illicit drugs. Use of medical cannabis is not exclusionary.

	27. Participation in any other investigational drug or device trial in which administration of an investigational study drug/device occurred within 30 days or placement of a non-drug eluting medical device within 15 days prior to the Screening Visit (Visit 1). 28. In the opinion of the investigator, participant has any disorder or finding that might interfere with the conduct of the study.
TEST PRODUCT	Name: DARE-VVA1 (tamoxifen vaginal insert) 1, 5, 10, and 20 mg Dose, route: 1, 5, 10, and 20 mg; vaginal administration by self-placement
CONTROL PRODUCT	Name: Matching placebo vaginal insert Dose, route: vaginal administration by self-placement
TREATMENT REGIMENS	DARE-VVA1 and placebo inserts will be self-administered by participants for 56 days (Days 1 to 56). The IP will be inserted intravaginally in the morning, at approximately the same time. Treatment will be administered once a day for the first 2 weeks, followed by twice weekly treatment for 6 weeks. The first twice-weekly dose will be administered on Day 18 during a study visit.
PLANNED STUDY SITES	Approximately 3 study sites in Australia.
CRITERIA FOR EVALUATION	Pharmacokinetics: After baseline evaluations including the time 0 venous plasma sample, the Day 1 DARE-VVA1 dose or matching placebo will be administered. Serial peripheral venous samples will be drawn from an indwelling line at 0.5, 1, 2, 4, 5, 8, 12, and 24 hours. The same sampling schedule will be used for PK analysis with administration of the Day 56 vaginal insert. Trough samples will be collected before administration of inserts on Days 4, 7, 10, 18, 28, and 42, and a final sample will be collected at follow-up on Day 63. Samples will be analyzed using validated methods to determine plasma concentrations of tamoxifen and 3 metabolites: 4-hydroxytamoxifen, N-desmethyltamoxifen, and N-desmethyl-4-hydroxytamoxifen (endoxifen). Safety: Observations of safety (self-reported or by examination) will be recorded on an ongoing basis. Any irritation, discharge or pain will be reported as an adverse event (AE) using standardized Medical Dictionary for Regulatory Activities (MedDRA) codes and graded for severity. Visual examination by vaginal speculum and full pelvic examination for any vaginal inflammation will be conducted at screening, pretreatment (Day 1), during treatment, and 1 week after treatment. Clinical laboratory measurements including full hematology and biochemistry panels will be recorded at screening, at baseline, on Days 7, 18, 28, and 57, and 1 week after treatment. Dipstick urinalysis of a void sample will be reported at screening, at baseline, on Days 7, 18, 28, and 57, and 1 week after treatment. If abnormal, the sample will be centrifuged for microscopic description of cellular elements. Vital signs, including pulse rate, respiratory rate, and supine blood pressure, will be recorded in a supine position at screening, during the administration period, and 1 week after treatment. Standard 12-lead ECGs will be recorded at screening, prior to dose on Days 1, 7, 18, 28, and 56, at 4 hours postdose on Days 1 and 56, on Day 57, and 1 week after treatment.

	A complete physical examination (excluding rectal examinations) will be performed at screening and will include a manual breast examination. Subsequent physical examinations will be abbreviated and will be directed based on signs and symptoms exhibited by the participant. Pelvic speculum and visual examinations will be conducted to identify vaginal abnormalities. Clinically significant abnormal findings from the speculum examination will be reported as an AE. Investigators will also conduct an assessment of local irritation; erythema and edema will be rated from 0 (none) to 3 (severe). Women who have not undergone hysterectomy will have a transvaginal ultrasound to determine endometrial thickness. Pharmacodynamics and Efficacy: Estrogenic effect measurements will include vaginal cytology (maturation index; percentage of basal and superficial cells) and vaginal pH at screening and baseline, every 2 weeks during treatment, and 1 week after treatment. Pharmacodynamics will be assessed by correlating the dose administered to exposure of tamoxifen in plasma, and then by relating the exposure to local vaginal changes in cytology and pH as well as to the reported symptomatology over 56 days. Exploratory: Menopause-specific Quality of Life (MENQOL) questionnaires will be completed prior to dosing on Day 1, and after treatment on Day 57. Details of the analysis of the responses to the Usability and Acceptability questionnaire will be outlined in the statistical analysis plan.
STATISTICAL METHODS	**General:** For the purpose of all safety, efficacy, and other analyses where applicable, baseline is defined as the last measurement before the start of study drug administration. Continuous endpoints will be summarized with number (n), mean, standard deviation, median, minimum, and maximum. In addition, change from baseline values will be calculated at each time point and summarized descriptively. For categorical endpoints, descriptive summaries will include counts and percentages. **Analysis Populations:** The ITT population, defined as all randomized participants, will be used to summarize participant disposition, demographics and baseline characteristic summaries, efficacy endpoints, and exploratory endpoints. Efficacy evaluations include changes in vaginal pH, changes in vaginal cytology (maturation index; percentage of basal and superficial cells), change in dyspareunia, and change in most bothersome symptom. These will be summarized using the ITT population. For the analysis the exploratory endpoints, results from the MENQOL questionnaire and the Usability and Acceptability questionnaire will be summarized over time from baseline in the ITT population. An analysis of covariance (ANCOVA) model will be used to assess treatment differences in change from baseline for vaginal pH, vaginal cytology, and most bothersome symptom, using baseline score as a covariate. With no formal testing planned for this study, the *P* values will be informational. The Safety population, defined all participants who are enrolled and receive any amount of planned IP, will summarize the recorded AEs, clinical laboratory safety tests, vital signs, ECG results, physical examination findings, and any other parameter relevant for safety assessment.

	The PK population consists of all participants who receive at least 1 dose of IP and provide at least 1 quantifiable PK plasma sample. This population will be used to summarize PK concentrations and parameters over time. Pharmacokinetic parameter estimates will be calculated by a standard noncompartmental method of analysis; these may include (but are not limited to) measures of the extent of absorption using estimates of the area under the plasma concentration-time curve (AUC), the maximum observed drug concentration (C_{max}), and the time to reach maximum drug concentration (T_{max}). Other parameters may be included at the discretion of the pharmacokineticist and as data permit. Participant listings will be provided for all the CRF data.
SAMPLE SIZE DETERMINATION	This dose ranging study is not powered for statistical significance. A sample size of 8 participants in each treatment group is considered sufficient to provide information on safety, PK, and PD effects, to guide the design of future studies with DARE-VVA1. A total of 40 participants is planned for this study.
STUDY AND TREATMENT DURATION	The sequence and maximum duration of the study periods will be as follows: 1. Screening: 21 days 2. Treatment: 56 days 3. Follow-up: 7 days The maximum treatment duration for each participant is 56 days. The maximum study duration for each participant is approximately 12 weeks.

2.2. Schedule of Events

Table 2-1: Schedule of Events

	Screening	Administration Period																ET	FU
Day(s)	-21 to -1	1-2[a]					4[b]	7[a,b]	10[b]	18[b]	28[b]	42[b]	56-57[a]						63
Window	-	-					±1	±1	±1	±1	±1	±1	±1					-	±1
Time from Admin. (hr.)		Pre-dose	0	4	10	24[c]							Pre-dose	0	4	10	24[c]		
Informed consent	X																		
Inclusion/Exclusion	X																		
Medical history	X																		
Concomitant medications	X	X					X	X	X	X	X	X	X				X	X	X
Physical exam[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vaginal speculum exam[e]	X	X				X		X		X	X	X					X	X	X
Mammogram[f]	X																		
Cervical screening test[g]	X																		
Height and weight	X																		
Vital signs[h]	X	X		X	X	X		X		X	X	X	X		X	X	X	X	X
12-Lead ECG[i]	X	X		X				X		X	X		X		X		X	X	X
Serum biochemistry	X	X						X		X	X						X	X	X
Hematology	X	X						X		X	X						X	X	X
Urinalysis	X	X						X		X	X						X	X	X
Coagulation panel	X	X						X		X	X						X		X
TSH	X																		
FSH[j]	X																		
Drugs of abuse[k]	X																		
Viral serology[l]	X																		
Vaginal pH[m]	X	X								X	X	X					X	X	X
Vaginal cytology	X	X								X	X	X					X	X	X
Transvaginal ultrasound	X[n]																X	X	
Assessment of VVA symptoms[o]	X									X	X	X	X					X	X
Diary administration and review[p]	X	X					X	X	X	X	X	X	X					X	
Study drug administration[q]			X			X	X	X	X	X	X	X		X					
MENQOL		X															X	X	
Usability and Acceptability questionnaire						X						X					X	X	
PK blood samples[r]		X	0.5, 1, 2, 4, 5, 8, 12 (hr.)			X	X	X	X	X	X	X	X	0.5, 1, 2, 4, 5, 8, 12 (hr.)				X		X
AE[s]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE = adverse event; ECG = electrocardiogram; ET = early termination; FSH = follicle-stimulating hormone: FU = follow-up; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hr. = hour; IP = investigational product; MENQOL = Menopause-specific Quality of Life; PK = pharmacokinetics; TSH = thyroid-stimulating hormone; VVA = vulvar vaginal atrophy

a. Multiple non-PK assessments scheduled for the same time point should be performed on the same day as dosing. PK blood sample procedures should follow the defined window, if applicable.
b. Samples for PK trough levels should be obtained prior to DARE-VVA1 insertion on Days 4, 7, 10, 18, 28, and 42. Administration of DARE-VVA1 will take place at site on the day of these visits, after collecting the trough PK sample.
c. Participants will be discharged from the site after all 24-hour assessments have been completed. Day 1-2 only: Administration of DARE-VVA1 should be the final activity before discharge, following completion of all 24-hour assessments.
d. A complete physical examination (excluding rectal examinations) will be performed at screening and will include a manual breast examination. Subsequent physical examinations will be abbreviated and will be directed based on signs and symptoms exhibited by the participant.
e. Vaginal speculum examinations will include assessment of local irritation (scoring of erythema and edema), and a full pelvic examination.
f. Mammograms should be conducted ONLY in those participants who have not had one within the last 2 years.
g. Cervical screen testing should be conducted ONLY in those participants who have a cervix and have not had cervical screening within the last 5 years.
h. Vital signs assessments will include pulse rate, respiratory rate, and supine blood pressure. Assessments will be performed after the participant has been in a supine position for at least 5 minutes. Temperature will also be measured.
i. 12-lead ECGs will be performed after the participant has been supine for at least 5 minutes.
j. FSH will be assessed in all hysterectomized women who have not undergone bilateral oophorectomy, and in non-hysterectomized women who have not undergone bilateral oophorectomy and have experienced spontaneous amenorrhea for ≥ 6 months but < 12 months, to confirm postmenopausal status.
k. Drugs of abuse will be measured at screening by local laboratories via urinalysis and alcohol screens versus a commercially available urine dipstick.
l. Viral serology: a blood sample will be collected for the determination of HIV, HCV, and HBsAg.
m. Vaginal pH will be evaluated using commercially available pH strips.
n. Transvaginal ultrasound will be performed on women who have not undergone a hysterectomy. During screening, the pelvic examination, with assessment of local irritation and cervical screening (if needed), should be performed prior to the transvaginal ultrasound.
o. Participants will be required to engage in vaginal intercourse or other sexual activity (masturbation, etc.) at least 1 time between Days 49-56, and complete an assessment of VVA symptoms in their diary.
p. Diaries will be provided to participants at screening, and participants will be trained on their completion. Participants will record their administration of DARE-VVA1 in the diary, including the time of placement. Study staff should instruct participants to bring their diaries to all site visits for review.
q. On Days 4, 7, 10, 18, 28, and 42, participants should not self-administer the IP at home; blood samples for trough PK assessments should be collected at site before the IP is administered.
r. Permissible windows for PK sampling are as follows: 0.5 hours and 1 hours = ±10 minutes; 2, 4, 5, 8, 12, and 24 hours = ±15 minutes. Trough samples collected on Days 4, 7, 10, 18, 28, and 42 should be collected within 30 minutes before IP administration.
s. Adverse event information will be collected at the specified time points, as well as at any time when a clinical research unit staff member becomes aware of an AE during the administration period.

3. TABLE OF CONTENTS

3.1. List of In-text Tables

3.2. List of In-text Figures

AMENDED PROTOCOL

The following are the amended protocol and appendices.

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	EXPLANATION
λ_z	terminal rate constant
ADR	adverse drug reaction
AE	adverse event
AI	aromatase inhibitor
APTT	activated partial thromboplastin time
ATC	Anatomical Therapeutic Chemical
AUC	area under the plasma concentration-time curve
BMI	body mass index
BP	blood pressure
C_{max}	maximum observed plasma drug concentration
CRA	clinical research associate
CRF	case report form
CSR	clinical study report
CST	cervical screening test
DMP	data management plan
DVT	deep vein thrombosis
ECG	electrocardiogram
EDC	electronic data capture
eCRF	electronic case report form
FSH	follicle-stimulating hormone
FU	follow-up
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
hr.	hour
HR+	hormone receptor-positive
HREC	Human Research Ethics Committee
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
INR	International Normalized Ratio
IP	investigational product
ITT	intent-to-treat

ABBREVIATION	EXPLANATION
NYHA	New York Heart Association
MedDRA	Medical Dictionary for Regulatory Activities
MENQOL	Menopause-specific Quality of Life (questionnaire)
OTC	over-the-counter
Pap	Papanicolaou (test)
PD	pharmacodynamics
PE	pulmonary embolism
PK	pharmacokinetics
PT	prothrombin time
RBC	red blood cell
SADR	serious adverse drug reaction
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SERM	selective estrogen receptor modulator
THC	tetrahydrocannabinol
TIA	transient ischemic attack
$t_{1/2}$	plasma terminal half-life
T_{max}	time of occurrence of maximum observed plasma drug concentration
TSH	thyroid-stimulating hormone
UTI	urinary tract infection
VVA	vulvar and vaginal atrophy
WHO-DD	World Health Organization Drug Dictionary

5. INTRODUCTION

5.1. Background and Rationale

Vulvar and vaginal atrophy (VVA) is a common and underreported condition that is a result of decreased estrogenization leading to thinning of the vaginal epithelium.[1,2] Typical symptoms include vaginal dryness, itching, burning, and painful intercourse, adversely impacting quality of life. Clinical findings include the diagnostic presence of pale and dry vulvovaginal mucosa with petechiae, as well as a vaginal pH > 5. Vulvar and vaginal atrophy most commonly occurs in the postmenopausal phase, during which the prevalence is close to 50%.[3]

Over-the-counter (OTC) remedies such as vaginal moisturizers and lubricants can provide temporary symptomatic treatment at the time of use. Localized estrogen therapy (i.e., estrogen-containing creams, rings, and suppositories) can treat the underlying physiologic issue and is the most commonly prescribed treatment by physicians for VVA. However, this therapeutic approach is contraindicated for women with hormone receptor-positive (HR+) breast cancer. In addition to surgery and/or radiation, many of these women are treated with aromatase inhibitors (AIs), which deplete the body of estrogen and induce a menopausal state irrespective of age. Consequently, the prevalence of VVA in HR+ breast cancer survivors is an estimated 70%.[4,5] Although localized estrogen therapy is highly effective in reducing the symptoms of VVA in otherwise healthy women, it is a suboptimal intervention for HR+ patients and survivors because of the prolific response of these tumors to the presence of estrogen in the surrounding tissue. As a result of this safety concern, the current estrogen products on the market for the treatment of VVA are labeled as being contraindicated when the patient has a "known, suspected, or a history of breast cancer". Oncologists, obstetricians, gynecologists, and primary care providers are reluctant to prescribe any estrogen-based products owing to concerns of reintroducing estrogen into the system, despite the low dose and topical delivery.

Daré Bioscience, Inc. (Daré) is developing a novel local application of tamoxifen to mitigate the symptoms of VVA for patients with or at risk for HR+ breast cancer, including women currently on anticancer therapy. There remains a large unmet need for a novel nonhormonal VVA treatment specifically developed for this subset of cancer patients and survivors, and other women who require or prefer a treatment option that does not contain estrogen.

Selective estrogen receptor modulators (SERMs) represent an exciting new option for the treatment of VVA in an HR+ patient population. Tamoxifen is a well-known and well-characterized SERM that has been prescribed by oncologists for decades for the treatment of breast cancer. Tamoxifen acts as an estrogen antagonist in the breast; it binds estrogen receptors in the breast tissue, effectively blocking natural estrogen from binding to these sites, and is therefore an effective HR+ breast cancer treatment. In contrast, in other tissues such as uterine and vaginal tissues, tamoxifen acts as an estrogen agonist, producing similar physiological responses to those produced by estrogen, without being a true estrogen.

Studies of tamoxifen conducted over the last 40 years have documented the estrogen-like effects of this SERM on vaginal epithelium.[6-14] A preliminary clinical study of intravaginally administered tamoxifen in postmenopausal women further supports the potential for locally administered tamoxifen to have positive effects that counter VVA in the vaginal tissue without significant systemic absorption (see Section 5.3). Localized tamoxifen therapy thus has the potential to counter the physiologic changes that lead to VVA without introducing estrogen back into the system. Together, these studies establish a strong scientific rationale for the continued

development of DARE-VVA1, as a novel intervention expected to modulate the symptoms of VVA in an HR+ breast cancer population without the use of estrogen-based hormones.

5.2. Nonclinical Experience

Vaginal tamoxifen has been evaluated in rats and rabbits. In a 3-day repeat-dose study (Study 3015-001) in ovariectomized female rats, intravaginal tamoxifen was evaluated at doses of 0.2 mg/kg/day, 2.0 mg/kg/day, and 20 mg/kg/day.[15] No vaginal irritation was observed at any dose. A dose-dependent increase in uterine wet weight was observed at all dose levels, which correlated with luminal epithelial and myometrial hypertrophy and stromal hypertrophy/hyperplasia. Microscopic evaluation showed minimal to mild focal erosions in the vagina at the highest dose and mild epithelial hyperplasia at all doses. A 28-day study in rabbits (Study 2110-001) evaluated 2 doses (1 mg and 20 mg) of tamoxifen. Inappetence was observed, and body weight gain was reduced at 1.0 mg, while body weight loss was observed at 20 mg. No test article-related vaginal irritation was observed, with sporadic findings of erythema and edema comparable to those seen in vehicle-treated animals.

From previous studies in rabbits, the absorption of tamoxifen from the vagina is expected to be relatively rapid. In rabbits, the T_{max} was 0.5 to 1.0 hour following vaginal administration of 1.0 mg and 20 mg tamoxifen. As stated above, this formulation is designed to release tamoxifen rapidly following disintegration of the gelatin capsule. The time points in the DARE-VVA1-001 study were chosen to collect information over the time frame when plasma concentrations are expected to rise and reach a steady state. There are samples taken intensively over the first 24 hours and then periodically up to 8 weeks (56 days). Following oral administration of tamoxifen, T_{max} is about 5 hours. The present study will also examine PK during the time after the last dose intensely over 24 hours. As noted, tamoxifen has a long half-life following oral administration (5 to 7 days based on Nolvadex labeling[16], and its metabolites can have longer half-lives). Attempting to collect data through several half-lives following the last vaginal dose would unduly prolong the study and likely not provide any new information about tamoxifen. Nonetheless, the present amendment removes 3 sampling time points on Day 1 and Day 56 (i.e., samples at 3 hours, 6 hours, and 18 hours) since these are not expected to contribute to understanding of the pharmacokinetic profiles and parameters.

5.3. Clinical Experience

Daré's drug product DARE-VVA1 has not been tested before in humans. Previously, an exploratory study of vaginal tamoxifen has been conducted in 4 healthy postmenopausal women, in which a vaginal suppository containing 13 mg tamoxifen was formulated by a compounding pharmacist.[17] Participants self-administered the suppository once a day for 1 week, before moving to a twice-per-week schedule. Blood concentrations of tamoxifen were measured at 8 weeks, with samples collected 5 hours after insertion. Additional assessments included measurements of vaginal pH and improvement of vaginal dryness, and monitoring of adverse events (AEs).

After 3 months of treatment, the median vaginal pH was 5.0 (range: 5.0 to 5.2), compared to 7.1 (range: 6.5 to 7.5) at baseline, with a median paired difference of 2.0 (range: 2.5 to 1.5). Self-assessments of dryness using a visual analog scale from 0 (participant not bothered by dryness) to 10 (participant extremely bothered by dryness) showed an improvement, from a median score of 8 (range: 7.5 to 9.0) at baseline to 3.0 (range: 2.0 to 3.0) after 3 months, with a median paired difference of 5.5 (range: 6.0 to 4.5).

All 4 participants completed the 3-month treatment period. No AEs were reported, and there were no changes to vital signs. Measurements of blood concentrations of tamoxifen at 8 weeks were conducted for all 4 participants; the median plasma concentration of tamoxifen was 5.8 ng/mL (range: 1.0 to 10.0 ng/L). In comparison, after once daily oral treatment with 20 mg tamoxifen for 3 months, the average steady state plasma concentration of tamoxifen is 122 ng/mL (range 71.0 to 183.0 ng/mL).[16]

This exploratory study demonstrated that vaginal administration of tamoxifen represents a possible new treatment approach for postmenopausal women with VVA. With this route of administration, tamoxifen demonstrated clinically relevant physiological changes, while systemic absorption of the study drug was not clinically relevant, with systemic exposure less than 10% of that seen when the same dose is administered orally.[16] The local action of tamoxifen on the vaginal epithelium suggests that the parent compound itself is estrogenic and not metabolized locally in the vaginal epithelium, but predominantly systemically into anti-estrogens. Together, these results suggest that tamoxifen could be beneficial for the treatment of VVA in patients who are at risk of breast cancer, due to its local activity as an estrogen, and systemic activity as an estrogen antagonist.

5.4. Summary of Potential Risks and Benefits

The potential benefits of study participation are that participants with VVA may experience a reduction in the symptoms associated with VVA as a result of treatment with DARE-VVA1. No other benefits of participation are anticipated.

The potential risks of study participation include those associated with exposure to tamoxifen and the excipients found in DARE-VVA1 and the risks of medical evaluation, including venipuncture.

Oral tamoxifen (tablets or solution) is approved for the treatment of estrogen receptor-positive metastatic breast cancer and to reduce the risk of breast cancer in women at high risk.[18] The label includes a boxed warning concerning the risk of uterine malignancies, stroke, and pulmonary embolism. General warnings include risks of thromboembolic events (although this risk is greater when co-administered with chemotherapy), embryo-fetal toxicity (which is not a risk in the present study population), and liver cancer and liver abnormalities.

The National Surgical Adjuvant Breast and Bowel Project reported relative risks of serious events in a double-blind, placebo-controlled study of 5 years' treatment with tamoxifen (20 mg per day) designed to evaluate whether treatment would reduce the incidence of invasive breast cancer in high-risk women. After a median treatment duration of 3.5 years in 13,388 women, the rates (per 1,000 women per year) for major outcomes were as follows:

Major Outcomes	Rates for tamoxifen (per 1,000 women per year)	Rates for placebo (per 1,000 women per year)
Endometrial adenocarcinoma	2.20	0.71
Uterine sarcoma	0.17	0.0
Stroke	1.43	1.00
Pulmonary emboli	0.75	0.25
Deep vein thrombosis	1.26	0.79
Cataracts	25.41	22.51

Source: Soltamox label[18]

In addition to these serious risks, the most common adverse reactions with oral tamoxifen include hot flashes, mood disturbances, vaginal discharge, vaginal bleeding, nausea, and fluid retention.[18]

In the present study, steps will be taken to reduce the risks associated with the use of tamoxifen. In addition to limiting the treatment duration to 56 days, and to the reduction of systemic exposure afforded by the use of intravaginal administration, the present study has been designed with eligibility criteria that will exclude participants who might be at particular risk of experiencing the more serious side effects of tamoxifen, while regular safety monitoring will be performed. Eligible participants who have not undergone hysterectomy will have no history of endometrial ablation or endometrial hyperplasia, with ultrasound at screening showing endometrial thickness ≤ 4 mm. Participants with a cervix will also have an up-to-date cervical cancer screening record. All participants must have a normal mammogram within 2 years of screening; participants who have not had a mammogram in the last 2 years, or have a cervix but have not had a cervical screening test (CST) in the last 5 years, will be required to undergo these assessments during screening.

Participants will be excluded if they have any of the following: a history of coagulopathies, thrombophilia, thromboembolic disease, or significant transient ischemic attack; significant cardiac history; recent history of breast cancer (or suspicion of breast cancer), abnormal cervical screening result within 2 years; endometrial pathology; known or suspected estrogen-dependent neoplasia. Safety monitoring will include 12-lead electrocardiograms (ECGs) to evaluate possible cardiac problems; laboratory assessments will include measurement of liver functions tests and clotting parameters, to monitor hepatic safety and potential embolism/thrombotic events, respectively; and regular vaginal inspection. Due to the reported risks of endometrial adenocarcinoma and uterine sarcoma, transvaginal ultrasounds will be performed at screening on women who have not undergone hysterectomy in order to measure endometrial thickness.

In the present study, participants allocated to active treatment will receive tamoxifen intravaginally for 56 days, at doses ranging from 1 mg per day to 20 mg per day for 2 weeks, before moving to a twice-weekly regimen. Administration of tamoxifen by intravaginal inserts is expected to yield significantly lower systemic concentrations of tamoxifen than oral administration. In an exploratory study, 4 women were treated with vaginal suppositories containing 13 mg tamoxifen once daily for 1 week then twice a week thereafter. Participants' systemic plasma concentrations (sample taken 5 hours post last dose following 8 weeks of treatment) ranged from 1.0 to 10.0 ng/mL[17]; in comparison, an average steady-state concentration of 122 ng/mL was observed with 20 mg oral tamoxifen once daily for 3 months.[16]

Although long-term treatment with tamoxifen is associated with risks of serious adverse effects, the risks associated with 56 days' treatment with tamoxifen are considered minimal. In comparison, the potential reduction of VVA symptoms could be beneficial to participants, with these symptoms affecting numerous aspects of women's lives, such as sex life, self-esteem, and relationships, in addition to the improvement in physical health.[19]

A summary of the pharmaceutical properties and known potential risks of DARE-VVA1 is provided in the current version of the Investigator's Brochure (IB). The investigator must become familiar with all sections of the DARE-VVA1 IB before the start of the study.

6. OBJECTIVES

6.1. Primary Objective

The primary objectives are:

- To evaluate the safety and tolerability of DARE-VVA1 by intravaginal administration
- To determine the plasma pharmacokinetics (PK) of DARE-VVA1 after intravaginal application

6.2. Secondary Objectives

The secondary objective is:

- To evaluate preliminary efficacy and pharmacodynamics (PD) in terms of most bothersome symptom, dyspareunia, and changes in vaginal cytology and pH

6.3. Exploratory Objectives

The exploratory objective is:

- To evaluate the impact of DARE-VVA1 on quality of life using a menopause-specific instrument
- To assess the usability and acceptability of DARE-VVA1

6.4. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of DARE-VVA1 by intravaginal administration	• Adverse events • Clinical laboratory findings • Vital signs results • 12-lead ECG results • Physical examination findings • Change in local site irritation scores from baseline to Day 57 • Endometrial thickness (measured by transvaginal ultrasound) in women who have not undergone hysterectomy prior to the study
• To determine the plasma PK of DARE-VVA1 after intravaginal application	• Standard PK parameters from noncompartmental analysis on Day 1, with steady-state parameters on Day 56 • Dose-proportionality of tamoxifen

Secondary	
• To evaluate preliminary efficacy and pharmacodynamics of DARE-VVA1 in terms of most bothersome symptom, dyspareunia, and changes in vaginal cytology and pH	• Change of vaginal pH from baseline to Day 57 • Change in vaginal cytology (maturation index; percentage of basal and superficial cells) from baseline to Day 57 • Change in most bothersome symptom from baseline to Day 56 • Change in severity of dyspareunia from baseline to Day 56 • Correlation between exposure and local changes
Exploratory	
• To evaluate the impact of DARE-VVA1 on quality of life using a menopause-specific instrument • To assess the usability and acceptability of DARE-VVA1	• Change in the MENQOL questionnaire from baseline to Day 57 • Responses to the Usability and Acceptability questionnaire over time

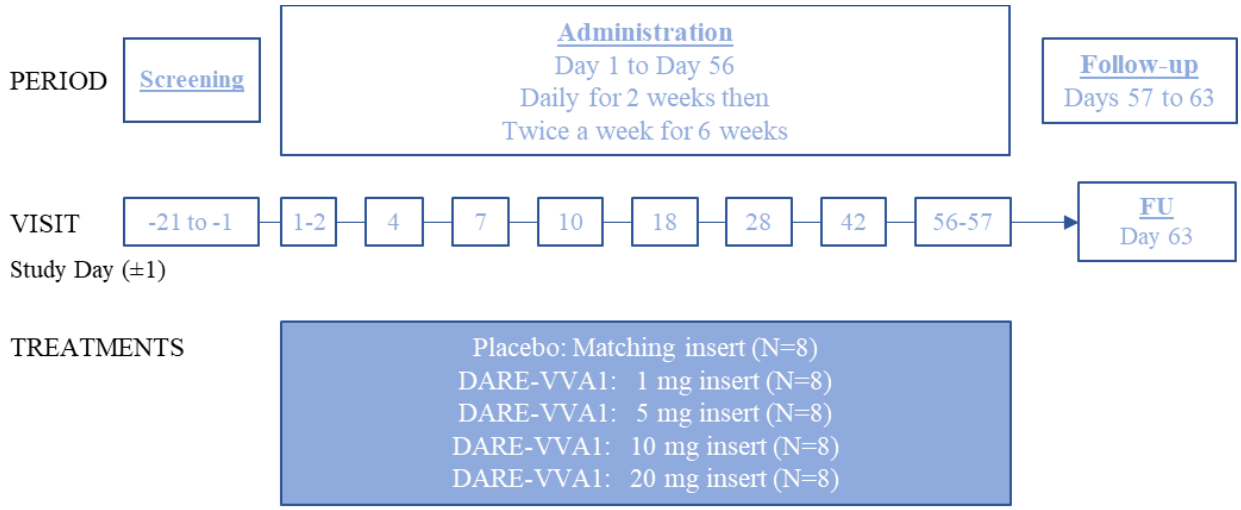
7. STUDY DESIGN

7.1. Overall Study Design and Plan

This is a Phase 1/2, randomized, multi-center, double-blind, parallel-arm, placebo-controlled, dose-ranging study to evaluate the safety, tolerability, PK, and PD of DARE-VVA1, a novel intravaginal tamoxifen product. The investigational product (IP) will be evaluated at 4 dose levels (1 mg, 5 mg, 10 mg, and 20 mg) and compared to a placebo vaginal insert. With each dose level, the IP will be administered intravaginally for 56 days, according to the following treatment schedule: once daily for 2 weeks then twice a week for 6 weeks.

Approximately 40 postmenopausal women, 20 who have undergone hysterectomy and 20 who have not, with VVA will be enrolled. After signing informed consent, eligible participants will be randomly allocated as follows: the 20 hysterectomized women will be allocated to 1 of the 5 treatment groups, and the 20 non-hysterectomized women will be randomly allocated to one of the same 5 treatment groups, such that each treatment group ends up with 4 hysterectomized women and 4 non-hysterectomized women, for a total of 8 women. (Figure 7-1).

Figure 7-1: Study Design



Abbreviations: D = day; FU = follow-up; N = number of participants

Participants must be healthy postmenopausal women aged 40 to 75 years (inclusive) and have moderate to severe VVA, as determined by a vaginal pH greater than 5 at the Screening Visit, ≤ 5% superficial cells on vaginal cytology, and either at least 1 moderate or severe symptom on self-assessment of i) vaginal dryness, ii) vaginal and/or vulvar irritation/itching, iii) dysuria, or iv) vaginal pain with sexual activity (dyspareunia), or the presence of vaginal bleeding associated with sexual activity. Participants are required to have a normal-appearing vagina upon speculum examination. Participants with a cervix are required to have a normal appearing cervix upon speculum examination, Participants who have not undergone hysterectomy are required to have an endometrial thickness ≤ 4 mm. All participants are required to have a recent normal mammogram and manual breast examination at screening. Mammograms and CSTs will be conducted for those

participants who have not had these tests in the timeframe indicated by the inclusion criteria. Participants will not be eligible if they have a medical history that suggests that they may be at risk of serious side effects of tamoxifen (e.g., thromboembolic disease, abnormal cervical screening results or history of endometrial pathology). Participants will also be excluded if they are receiving medications that could confound assessments (e.g., vaginal hormonal products, estrogen therapy, or use of SERMs or AIs within 6 months prior to screening) or have previously experienced an unsatisfactory outcome from a vaginal hormone therapy for VVA.

Preliminary efficacy will be assessed by vaginal cytology (for maturation index) and by vaginal pH, measured at baseline, every 2 weeks during treatment, following completion of treatment (Day 57), and at the follow-up visit conducted on Day 63. In addition, most bothersome symptom and dyspareunia will be evaluated during the treatment period and at follow-up. An exploratory assessment of quality of life will be conducted using the Menopause-specific Quality of Life (MENQOL) questionnaire, and participants will report on the usability and acceptability of DARE-VVA1 using a questionnaire.

In each treatment group, participants will have serial blood sampling for PK analysis, with venous samples drawn from an indwelling line. Dense sampling will be performed following the Day 1 and Day 56 administrations of DARE-VVA1; trough samples will be collected prior to dosing on Days 4, 7, 10, 18, 28, and 42, and a final sample will be collected at follow-up on Day 63. Samples will be analyzed using validated methods to determine plasma concentrations of tamoxifen and 3 metabolites: 4-hydroxytamoxifen, N-desmethyl-tamoxifen, and N-desmethyl-4-hydroxy-tamoxifen (endoxifen).

Safety will be assessed by evaluating AEs, vital sign measurements, clinical laboratory test results, 12-lead ECGs, and physical examination findings. In addition, vaginal speculum examinations will be performed, including an assessment of local irritation (in terms of erythema and edema). Women without a history of hysterectomy will undergo transvaginal ultrasounds at screening and at the end of treatment (Day 57).

Following the completion of treatment, participants will attend a follow-up visit on Day 63.

All AEs observed by the study personnel or reported by the participant during the study (from the time of the signing of the informed consent through the follow-up visit) will be documented.

7.2. Rationale and Discussion of Study Design

The use of estrogen-containing products for the treatment of VVA is contraindicated in women with HR+ breast cancer, due to their capacity to promote tumor growth. There remains a large unmet need for a novel nonhormonal VVA treatment for this subset of cancer patients and survivors, and other women who require or prefer a treatment option that does not contain estrogen. An exploratory study of intravaginal tamoxifen has demonstrated the potential for this SERM, which acts as an estrogen receptor agonist in the vagina and as an antagonist in breast tissue, to improve VVA symptoms (vaginal pH and patient-reported dryness). In addition, plasma concentrations of tamoxifen were considerably lower than those seen with oral administration.

The present study is the first clinical evaluation of DARE-VVA1, a GMP-manufactured tamoxifen vaginal insert intended for self-placement. The study will evaluate 5 parallel groups of 8 patients, randomizing participants to receive DARE-VVA1 at 1 of the 4 dose levels or placebo. The double-blind, placebo-controlled, randomized study is a gold standard for clinical studies, and is considered suitable for the present study where the placebo vaginal inserts are identical to the

DARE-VVA1 inserts. Inclusion of a matched placebo will allow the distinction between adverse effects caused by tamoxifen and those that can be attributed to excipients or to mechanical effects due to the presence of an insert.

The study will be conducted in postmenopausal women with VVA, allowing a preliminary investigation of the PD of the IP in the target population. Eligibility criteria have been designed to exclude participants who might be at risk of the serious, albeit rare, side effects associated with tamoxifen such as thromboembolic effects and endometrial cancer; the short duration of the study will also reduce these risks, which are typically associated with long-term tamoxifen use.[18]

7.3. Selection of Doses in the Study

The present study will evaluate intravaginal tamoxifen at doses of 1, 5, 10, and 20 mg for 56 days, with participants in a control group receiving matching placebo. An exploratory study of vaginal tamoxifen suppositories used a dose of 13 mg tamoxifen, which is similar to the daily dose of oral tamoxifen as used in estrogen receptor-positive breast cancer (20-40 mg).[17,18] Given that vaginal administration allows distribution of tamoxifen directly to the site of action, 20 mg tamoxifen will be the highest dose studied here. Nonclinical studies evaluating 20 mg intravaginal tamoxifen in rabbits for 28 days showed no significant effects on the reproductive tract.

Inclusion of lower doses (1, 5, and 10 mg) may allow the identification of a maximally effective dose below 20 mg, allowing the use of a lower dose of tamoxifen, which could be beneficial when used long-term, particularly as this would be expected to reduce the risk of serious side effects.

The treatment schedule in the present study comprises treatment once daily for 2 weeks followed by 6 weeks on a twice-per-week schedule. This schedule is commonly used for intravaginal estrogen products.

7.4. Study Sites

The study will take place at approximately 3 sites in Australia. Each site is anticipated to screen sufficient participants to randomize a total of approximately 40 participants. A study site with a high recruitment rate may be allowed to recruit more participants if other sites have slow enrollment.

7.5. End of Study Definition

A clinical trial is considered completed when the last participant's last study visit has occurred.

8. PARTICIPANT POPULATION

8.1. Selection of Study Population and Diagnosis

This study will enroll sufficient postmenopausal female participants with moderate to severe VVA to randomly allocate 40 participants, 20 who have undergone hysterectomy and 20 who have not, to receive treatment with DARE-VVA1 (4 dose levels) or placebo, as shown in Figure 7-1.

Participants who do not meet all the eligibility criteria will not be enrolled.

8.2. Study Entry Criteria

Participants must meet all inclusion criteria to be eligible for enrollment into the study.

Participants will not be eligible for entry into this study if they meet any of the exclusion criteria and will be discontinued at the discretion of the investigator in consultation with the medical monitor if they develop any of the exclusion criteria during the study.

8.2.1 Inclusion Criteria

Participants must meet all inclusion criteria to be eligible for enrollment into the study.

1. Women aged 40-75 (inclusive).
2. Postmenopausal women with a body mass index (BMI) between 18 and 38 kg/m^2, inclusive.
3. Postmenopausal, defined as:
    a. For non-hysterectomized women, 12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhea with serum follicle-stimulating hormone (FSH) levels > 40 mIU/mL or 6 weeks postsurgical bilateral oophorectomy.
    b. For hysterectomized women, serum follicle-stimulating hormone (FSH) levels > 40 mIU/mL or 6 weeks postsurgical bilateral oophorectomy
4. Have moderate to severe VVA as determined by self-assessment of the following symptoms: vaginal dryness, vaginal and/or vulvar irritation/itching, dysuria, vaginal pain with sexual activity (dyspareunia) (all self-assessed as none, mild, moderate, or severe), or vaginal bleeding associated with sexual activity (self-assessed as presence versus absence). To be eligible, at least 1 of the first 4 symptoms must be reported as moderate or severe, or vaginal bleeding associated with sexual activity must be present.
5. Women who currently have vaginal intercourse or other sexual activity (masturbation, etc.) at least once a month (with or without a partner), or who had intercourse or other sexual activity at least once a month in the past, but later decreased sexual activity due to excessive pain or vaginal dryness. Participants must be willing to engage in vaginal intercourse or other sexual activity (masturbation, etc.) at least 1 time between Days 49-56 of the clinical study.
6. Participants, upon pelvic examination with speculum examination, must have a normal-appearing vulva other than atrophic changes, and normal-appearing vagina (without erosions, ulcerations, scarring, or evidence of dermatoses) other than atrophic changes (loss of rugae, mucosal pallor, mucosal dryness, mucosal petechiae). Women without a cervix must have a normal-appearing vaginal cuff.

7. Women who have not undergone hysterectomy must have:
    a. No prior history of endometrial ablation.
    b. Endometrial thickness ≤ 4 mm on transvaginal ultrasound.
8. Women with a cervix must:
    a. Have a normal appearing cervix other than atrophic changes (i.e., cervical stenosis and/or flushness with the vaginal wall)
    b. Be current on all recommended screening and management requirements for cervical cancer.
9. Vaginal cellular cytology with ≤ 5% superficial cells.
10. Vaginal pH > 5 at Screening Visit.
11. Normal mammogram report within 2 years of screening.
12. Normal manual breast examination by investigator at baseline.
13. Baseline hematology, clinical chemistry, urinalysis, coagulation, and viral serologies for human immunodeficiency virus (HIV), hepatitis C virus (HCV), and hepatitis B surface antigen (HBsAg) all within normal limits OR accepted by the investigator and medical monitor as not clinically significant.
14. Normal 12-lead ECG.
15. Able to read, understand, and provide written informed consent and applicable data protection authorization after the nature of the study has been fully explained, and must be willing to comply with all study requirements.
16. Willing and able to correctly and independently complete all study procedures.

8.2.2 Exclusion Criteria

Participants will not be eligible for entry into this study if they meet any of the following exclusionary criteria:

1. A history of or physical examination finding for any significant cardiovascular, renal, pulmonary, neurological and hepatic diseases preventing compliance with this study.
2. A medical history of or use of anticoagulant drugs to treat or prevent coagulopathies, thrombophilia or thromboembolic disease (deep vein thrombosis, pulmonary or systemic embolism, stroke, or transient ischemic attack).
3. Uncontrolled hypertension (either systolic > 180 mmHg or diastolic > 105 mmHg), treatment with Class 1 antiarrhythmics or digitalis, history of congestive heart failure (New York Heart Association [NYHA] > Class I), or myocardial infarction within 12 months.
4. Women with a cervix cannot have had an abnormal CST within 2 years of screening. Participants can have atypical squamous cells of undetermined significance if human papilloma virus-negative.
5. Women who have not undergone hysterectomy cannot have a history of or current endometrial pathology: hyperplasia, carcinoma and/or polyp (prior history of a benign endometrial polyp with no current evidence of polyp is acceptable).

6. A medical history of breast cancer within 5 years of screening.

   Participants with a history of breast cancer more than 5 years prior to screening are considered eligible if their disease was node-negative, nonmetastatic, and if all treatment with aromatase inhibitors (AIs) or SERMs was completed at least 6 months prior to screening.
7. A medical history of malignant melanoma.
8. Any cancer (except nonmelanomatous skin cancer) diagnosed less than 5 years prior to the Screening Visit.
9. A medical history of undiagnosed vaginal bleeding.
10. A known or suspected estrogen-dependent neoplasia.
11. Previous radiation treatment to the pelvis.
12. Women who have previously reported an unsatisfactory outcome from a vaginal hormone therapy for VVA.
13. Known hypersensitivity to any ingredients in DARE-VVA1.
14. Use of vaginal hormonal products (rings, creams, gels, tablets, capsules) within 4 weeks prior to Day 1.
15. Use of transdermal estrogen products within 4 weeks prior to Day 1.
16. Use of oral estrogen therapy within 8 weeks prior to Day 1.
17. Use of estrogen-alone injectable drug therapy within 12 weeks prior to Day 1.
18. Administration of estrogen pellet therapy within 6 months prior to Day 1.
19. Use of thyroid hormone replacement therapy unless the participant is on a stable dose for > 6 months, and participant is euthyroid based on a normal, sensitive immunoassay for thyroid-stimulating hormone (TSH).
20. Use of SERMs or AIs within 6 months prior to screening.
21. Use of anabolic or other steroids (including hormonal creams such as testosterone) within 4 weeks prior to Day 1.
22. Use of corticosteroids, > 5 mg/day prednisone or equivalent, for more than 4 weeks within 4 weeks prior to Day 1.
23. Participants with any self-reported active sexually transmitted disease and/or evidence of infection (including bacterial vaginosis) on vaginal examination by the investigator.
24. Participants with a urinary tract infection during screening as assessed by urine dipstick test with abnormal test findings (any positive result for leukocytes AND any positive result for nitrites).
25. Women who have not undergone hysterectomy cannot have clinically significant uterine fibroids.
26. Evidence of current alcohol or drug abuse in the past 60 days, including a positive result from the urine drugs of abuse or alcohol screen, or history of drug or alcohol dependence

in the last 2 years, as assessed by the investigator. Alcohol abuse is defined as greater than 14 standard units/week for females, and drug abuse is defined as known psychiatric or substance abuse disorder that would interfere with participation with the requirements of this study, including current use of any illicit drugs. Use of medical cannabis is not exclusionary.

27. Participation in any other investigational drug or device trial in which administration of an investigational study drug/device occurred within 30 days or placement of a non-drug eluting medical device within 15 days prior to the Screening Visit (Visit 1).
28. In the opinion of the investigator, participant has any disorder or finding that might interfere with the conduct of the study.

8.3. Premature Participant Withdrawal

All participants will be advised that they are free to withdraw from participation in this study at any time, for any reason, and without prejudice. The investigator should make every reasonable attempt to keep participants in the study; however, participants must be withdrawn from the study if they withdraw consent to participate. Investigators must attempt to contact participants who fail to attend scheduled visits by telephone or other means to exclude the possibility of an AE being the cause of withdrawal. Should this be the cause, the AE must be documented, reported, and followed as described in Section 11.2.

The sponsor reserves the right to request the withdrawal of a participant due to protocol deviations or other reasons.

The investigator also has the right to withdraw participants from the study at any time for lack of therapeutic effect that is intolerable or otherwise unacceptable to the participant, for intolerable or unacceptable AEs, intercurrent illness, noncompliance with study procedures, administrative reasons, or in the investigator's opinion, to protect the participant's best interest.

If a participant is withdrawn before completing the study, the reason for withdrawal and the date of discontinuation will be recorded on the appropriate page of the case report form (CRF) or electronic case report form (eCRF). Whenever possible and reasonable, the evaluations shown in the Early Termination Visit in the schedule of events (Table 2-1) should be performed at the time of premature discontinuation.

8.4. Discontinuation of Investigational Product

Discontinuation from the IP does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the schedule of events (Table 2-1). If a clinically significant finding is identified (including, but not limited to, changes from baseline) after enrolment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an AE.

Participants who are not willing to complete the remaining study procedures indicated in the schedule of events (Table 2-1) after discontinuing study treatment should complete the procedures indicated for the Early Termination Visit at a minimum.

8.5. Participant Discontinuation/Withdrawal from the Study

Participants are free to discontinue the study at any time, for any reason, and without prejudice to further treatment. The investigator may remove a participant if, in the investigator's judgment,

continued participation would pose an unacceptable risk to the participant or to the integrity of the study data. All procedures for early termination must be completed. Reasons for removal or withdrawal may include:

- Withdrawal of consent
- Administrative decision by the investigator or sponsor
- Ineligibility
- Significant protocol deviation
- Participant noncompliance
- Safety concern by the investigator or sponsor
- Lost to follow-up

Participants who are withdrawn prior to completing all study visits may be replaced.

In the event of a participant's withdrawal, the investigator will promptly notify the sponsor and medical monitor and will make every effort to complete the Early Termination Visit assessments (Section 10.2.3). All withdrawn participants with ongoing clinically significant clinical or laboratory findings will be followed until the finding is resolved or medically stable; reasonable attempts will be made to follow-up with participants.

9. TREATMENTS

9.1. Identification of Investigational Products

DARE-VVA1 will be provided in the form of vaginal inserts. The vaginal route allows direct delivery of tamoxifen to the site of action and will reduce systemic exposure to tamoxifen.

DARE-VVA1 will be supplied as 1 mg, 5 mg, 10 mg, and 20 mg vaginal inserts by Catalent Pharma Solutions (St. Petersburg, Florida, USA).

Matching placebo (also supplied by Catalent Pharma Solutions) will be identical in appearance, smell, and feel.

9.2. Selection of Timing of Dose for Each Participant

The 1 mg, 5 mg, 10 mg, and 20 mg dose levels and placebo will be evaluated in parallel. Participants will be randomly allocated to receive treatment in 1 of the 5 treatment groups shown in Table 9-1. All participants will receive treatment with the IP for a total of 56 days.

Table 9-1: Study Design – Treatment Groups

Dose Level	Treatment	Number of Participants
Placebo	One placebo insert	N=8
1 mg	One DARE-VVA1 1 mg insert	N=8
5 mg	One DARE-VVA1 5 mg insert	N=8
10 mg	One DARE-VVA1 10 mg insert	N=8
20 mg	One DARE-VVA1 20 mg insert	N=8

The DARE-VVA1 (or placebo) vaginal insert will be inserted by the participant in the morning. Participants should make every effort to ensure that inserts are inserted at approximately the same time for each administration except on visit days when IP should be inserted after trough PK sample collection.

Participants will be instructed on how to correctly self-administer the IP on Day 1, at the time of the first administration, and a warning should be given that the insert should not be pushed up too close to the cervix.

On Days 1 and 56, blood samples for PK analysis will be collected immediately before administration of the IP, and at scheduled intervals after administration in accordance with the sampling schedule defined in the schedule of events (Table 2-1). In addition, blood samples should be collected within 30 minutes before administration of DARE-VVA1 on Days 4, 7, 10, 18, 28, and 42. A final sample will be collected at follow-up on Day 63.

9.3. Dose Adjustment Criteria

Dose adjustment is not allowed in this study.

9.4. Treatment Compliance

Participants will be instructed on how to correctly self-administer the IP on Day 1, at the time of the first administration.

Throughout the 56-day administration period, participants will be asked to record their administration of DARE-VVA1 on a paper diary, including the time of placement. Deviations from the planned doses (missed dose or timing) will be recorded on the participant's eCRF. Study personnel will review diaries at each visit, and diaries will be collected as source documents. Information from participant diaries will be transcribed on the appropriate eCRF pages for documentation of participant compliance with the IP.

9.5. Method of Assigning Participants to Treatment Groups

In this parallel-group randomized study, participants who meet study entry criteria will be randomly assigned in a 1:1:1:1:1 ratio, by history of hysterectomy, to 1 of the 5 treatment groups indicated in Table 9-1. The randomization schedule will be computer-generated using a permuted block algorithm and will randomly allocate IP to randomization numbers. Study center will not be a blocking factor in the randomization schedule. The randomization numbers will be assigned sequentially by a member of the ICON Clinical Research Team who is not otherwise involved in the study. Contact details for obtaining randomization numbers are provided in the Study Reference Manual. The randomization schedule will be prepared by ICON Clinical Research before the start of the study. No one involved in the study performance will have access to the randomization schedule before official unblinding of treatment assignment. No participant will be randomized into this study more than once.

9.6. Blinding and Unblinding Treatment Assignment

The different tamoxifen-dose DARE-VVA1 vaginal inserts and placebo are indistinguishable by appearance, smell, and feel.

All participants, investigators, and study personnel involved in the conduct of the study, including data management, will be blinded to treatment assignment with the exception of a specified unblinded statistician from ICON Clinical Research who will have access to the randomization code. The unblinded study personnel will not participate in study procedures or data analysis prior to unblinding of the study data to all study-related personnel.

Study personnel will make every effort to safeguard the integrity of the study blind to minimize bias in the conduct of the study. Treatment unblinding is discouraged if knowledge of the treatment assignment will not materially change the planned management of a medical emergency. Unblinding will be permitted in a medical emergency that requires immediate knowledge of the participant's treatment assignment.

Unblinding should be discussed in advance with the medical monitor, if possible. For emergency unblinding, study personnel will contact the ICON Clinical Research Team. Contact details are provided in the Study Reference Manual. If the investigator is not able to discuss treatment unblinding in advance, then they must notify the medical monitor as soon as possible about the unblinding incident without revealing the participant's treatment assignment.

The investigator or designee must record the date and reason for treatment unblinding on the appropriate CRF for that participant. In all cases that are not emergencies, the investigator must discuss the event with the medical monitor prior to unblinding the participant's treatment assignment.

If treatment assignment is unblinded for an individual participant, study personnel will be notified of that participant's treatment assignment without unblinding the treatment assignments for the

remaining participants in the study. Thus, the overall study blind will not be compromised. If a participant's treatment assignment is unblinded, she may or may not be asked to withdraw from the study. The investigator will make this decision after consultation with the medical monitor.

Overall unblinding will take place at the end of the study only after database lock has been achieved.

9.7. Permitted and Prohibited Therapies

All concomitant medications used (including OTC medications and herbal supplements) will be recorded in the source document and on the appropriate eCRF.

9.7.1 Permitted Therapies

With the exception of all prohibited therapies (see Section 9.7.2), the use of concomitant medications is allowed, but should be limited to those medications considered necessary.

The use of vaginal lubricants is permitted; however, they should not be used within 6 hours of administration of the IP.

9.7.2 Prohibited Therapies

The following therapies are prohibited both during the study and in the period before the study as shown:

- use of anticoagulant drugs to treat or prevent coagulopathies, thrombophilia, thromboembolic disease, or transient ischemic attack
- radiation treatment to the pelvis
- vaginal hormonal products (rings, creams, gels, tablets, capsules) (within 4 weeks prior to Day 1)
- transdermal estrogen products (within 4 weeks prior to Day 1)
- oral estrogen therapy (within 8 weeks prior to Day 1)
- estrogen-alone injectable drug therapy (within 12 weeks prior to Day 1)
- estrogen pellet therapy (within 6 months prior to Day 1)
- thyroid hormone replacement therapy is prohibited unless the participant has been on a stable dose for > 6 months, and is euthyroid based on a normal, sensitive immunoassay for TSH
- SERMS or AIs (within 6 months prior to Day 1)
- anabolic or other steroids (including hormonal creams such as testosterone) (within 4 weeks prior to Day 1)
- corticosteroids, > 5 mg/day prednisone or equivalent, for more than 4 weeks within 4 weeks prior to Day 1
- investigational drug (within 30 days prior to screening) or non-drug eluting medical device (within 15 days prior to screening)

The following therapies are prohibited during the study:

- intravaginal products (e.g., Femring® [estradiol acetate vaginal ring], ESTRING® [estradiol vaginal ring]) or medication, OTC or prescription

  NOTE: the use of vaginal lubricants is permitted, but not within 6 hours of administration of the IP

- consumption of St John's Wort (hypericum perforatum) and grapefruit, Seville (bitter) orange, and pomelo fruit/juice/preserves

- the following CYP3A4/5 inducers and CYP2D6 inhibitors are prohibited:

CYP3A4/5 inducers	**CYP2D6 inhibitors**
Apalutamide (strong), aprepitant, armodafinil	Abiraterone, amiodarone
Bosentan (moderate)	Bupropion (strong)
Carbamazepine (strong), corticosteroids	Celecoxib, cinacalcet (moderate), cobicistat
Dabrafenib	Duloxetine (moderate)
Efavirenz (moderate), encorafenib, enzalutamide (strong), etravirine (moderate)	Fluoxetine (strong)
Loriatinib (moderate), lumacaftor (strong)	Methadone, mirabegron (moderate)
Modafinil (moderate)	Paroxetine (strong)
Nevirapine	Terbinafine (strong)
Phenobarbital, phenytoin (strong)	
Rifabutin, rifampicin (strong), ritonavir, rufinamide	
Tipranavir	
Vemurafenib	

Participants receiving excluded therapies will be ineligible for study enrollment or for continuation in the study, at the discretion of Daré Bioscience Inc. and/or designee.

9.7.3 Restrictions

Participants will be required to engage in vaginal intercourse or other sexual activity (masturbation, etc.) at least 1 time between Days 49-56 of the clinical study (see Section 10.3.3.3 for details).

9.8. Treatment After End of Study

After the end of the study, each participant will be treated according to standard clinical practice.

9.9. Dispensing and Storage

The IP manufactured by Catalent Pharma Solutions (DARE-VVA1 and placebo) and supplied by PCI is to be used exclusively in the clinical study according to the instructions of this protocol.

The investigator is responsible for dispensing the IP according to the dosage scheme and for ensuring proper storage of the IP.

The investigator must confirm the receipt of the IP with his or her signature. A copy of this receipt must be kept by the investigator and another copy will be stored at Daré Bioscience Inc and/or ICON Clinical Research. Until the IP is dispensed to the participants, it must be stored at controlled room temperature (20 to 25°C, with excursion allowed from 15 to 30°C) in a securely locked area that is not generally accessible.

The key to the storage area is to be kept by the investigator or designee responsible for the IP. The store will be accessible only to those persons authorized by the investigator to dispense the IP.

Following dispensing, participants must store the IP at room temperature in a cool, dark, dry place. The IP should be kept out of reach of children.

9.10. Drug Accountability

The investigator must maintain adequate records showing the receipt, dispensing, return, or other disposition of the IPs, including the date, quantity, batch or code number, and identification of participants (participant number) who received the IPs. The investigator will not supply the IP to any person except those named as subinvestigators, designated study personnel, and participants in this study. The investigator will not dispense the IPs from any study sites other than those listed. The IPs may not be relabeled or reassigned for use by other participants. If any of the IPs are not dispensed, are lost, stolen, spilled, unusable, or are received in a damaged container, this information must be documented and reported to the sponsor and appropriate regulatory agencies, as required.

Upon completion of the study, the IPs (partly used, unused, and empty packaging) must be left in the original packaging and returned to the sponsor or designee for destruction.

9.11. Labeling and Packaging

Labeling and packaging of DARE-VVA1 and placebo will be performed by PCI (Port Melbourne, Victoria, Australia), and will comply with all applicable local regulations.

Details regarding IP packaging, labeling, and use instructions will be provided in a separate Study Reference Manual.

Investigators should save all empty packaging or packaging containing unused vaginal inserts for final disposition by the sponsor or contract pharmacy.

10. STUDY PROCEDURES

Participants must provide written informed consent before any study-related procedures are initiated, including the cessation of prohibited concomitant therapy.

For the timing of assessments and procedures throughout the study, refer to the schedule of events (Table 2-1). Throughout the study, every reasonable effort should be made by study personnel to follow the timing of assessments and procedures in the schedule of events for each participant. If a participant misses a study visit for any reason, the visit should be rescheduled as soon as possible.

10.1. Study Duration

10.1.1 Overall Study Schedule

The planned sequence and maximum duration of the study periods will be as follows:

1. Screening: 21 days
2. Treatment: 56 days
3. Posttreatment: 7 days

The maximum treatment duration for each participant is approximately 56 days.

The maximum study duration for each participant is approximately 12 weeks.

10.2. Study Periods and Visits

10.2.1 Screening

The participant must be screened within 21 days before enrollment in the study. Assessments to be conducted during screening are shown in the schedule of events (Table 2-1). No study-specific assessments should be conducted until the participant has provided written informed consent (see Section 14.4.1).

Participants who have not had mammograms and CSTs in the timeframe indicated by the inclusion criteria will undergo these assessments during screening.

Procedures for rescreening participants who initially fail to meet study entry criteria are described in Section 14.3.

10.2.2 Double-blind Treatment Period

The treatment period is defined as the period from Day 1 to Day 57, covering the 24-hour period after the final administration of the IP on Day 56.

Participants will self-administer DARE-VVA1 or placebo as instructed between Days 1 and 56, in accordance with the treatment group to which they are allocated.

Study assessments will be conducted in accordance with the schedule of events (Table 2-1).

10.2.2.1 Day 1 to 2

The Day 1 to Day 2 visit will be an overnight stay at the study site. Participants will attend the study site on the morning of Day 1.

Participants will be instructed on how to correctly self-administer the IP at the time of the first administration, and a warning should be given that the insert should not be pushed up too close to the cervix.

Samples for analysis of tamoxifen PK will be collected before administration of the IP and at the scheduled times indicated in the schedule of events (Table 2-1) and in Section 10.3.2.1.2. Where multiple assessments are scheduled for the same time point, assessments should be performed within 15 minutes of the scheduled time with priority given to any PK blood sample procedures, if applicable.

Participants will be provided with a diary in which to record their administration of DARE-VVA1, including the time of placement, and will be trained on its completion. Study staff should instruct participants to bring their diaries to all site visits for review. Diaries will be completed at site on days where DARE-VVA1 is administered at site.

On Day 2, after participants have provided the 24-hour PK sample, a vaginal speculum examination will be conducted before the participant self-administers the second IP insert.

Participants will be discharged from the study site on Day 2, following collection of the 24-hour PK sample and completion of all 24-hour assessments and insertion of the second IP insert. At discharge, participants will be provided with sufficient IP to last for the 56-day treatment period.

10.2.2.2 Days 4, 7, 10, 18, 28, and 42

Participants will return to the study site on Days 4, 7, 10, 18, 28, and 42, to complete the procedures shown in the schedule of events (Table 2-1).

On Days 4, 7, 10, 18, 28, and 42, participants should not self-administer the IP at home; blood samples for trough PK assessments should be collected at site within 30 minutes before the IP is administered.

Participants will be required to bring their diaries to each of these visits.

10.2.2.3 Day 56 to 57

The Day 56 to Day 57 visit will be an overnight stay at the study site. Participants will attend the study site in the morning of Day 56. Participants should not self-administer the IP at home on Day 56; the IP will be administered at the site as instructed. Any unused IP should be returned to the study site.

Samples for analysis of tamoxifen PK will be collected before administration of the IP and at the scheduled times indicated in the schedule of events (Table 2-1) and in Section 10.3.2.1.2. Where multiple assessments are scheduled for the same time point, assessments should be performed within 15 minutes of the scheduled time with priority given to any PK blood sample procedures, if applicable.

Participants will be discharged from the study site after completion of all 24-hour assessments noted on Day 57.

10.2.3 Early Termination Visit

Participants who discontinue treatment with the IP before Day 56 should remain on study (see Section 8.4), and the remaining study procedures should be completed as indicated by the schedule of events (Table 2-1). Participants who are not willing to complete the remaining study procedures indicated in the schedule of events after discontinuing study treatment should complete the procedures indicated for the Early Termination Visit at a minimum.

Participants should return all unused IP and their participant diaries.

10.2.4 Day 63 Follow-up Evaluation

At 7 days after the last administration of the IP, the participants will return to the study site for a follow-up visit. Safety and efficacy assessments will be conducted in accordance with the schedule of events (Table 2-1), and a final PK sample will be collected.

10.3. Assessments

10.3.1 Safety Variables

Safety assessments will include the evaluation of AEs, clinical laboratory assessments, vital signs, 12-lead ECGs, physical examinations, vaginal speculum examinations, and transvaginal ultrasounds.

10.3.1.1 Clinical Laboratory Safety Assessments

10.3.1.1.1 Clinical Laboratory Tests to be Performed

Samples for the following laboratory tests will be collected at the time points specified in the schedule of events (Table 2-1).

Hematology:	hemoglobin, hematocrit, red blood cell (RBC) count, RBC indices (mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, red blood cell distribution width), platelet count (or estimate), white blood cell count including differential
Serum Chemistry:	albumin, total bilirubin, total protein, calcium, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, creatinine, glucose, sodium, potassium, chloride, bicarbonate, lactate dehydrogenase, uric acid
Coagulation Panel:	PT, APTT, fibrinogen, INR
Urinalysis:	Leukocytes, nitrite, pH, specific gravity, blood, glucose, protein, ketones, bilirubin, urobilinogen
Viral Serology:	HIV, HCV, and HBsAg (screening only)

Urine Drug Screen:	Urine drugs of abuse according to the local standard (including, at a minimum, cocaine, tetrahydrocannabinol, amphetamines and opiates) via urinalysis conducted by local laboratories, and alcohol screens via a commercially available urine dipstick During the screening period, urine drugs of abuse and alcohol screens may not be repeated for eligibility unless the investigator believes that a positive result is possibly attributable to a concomitant medication; a repeat test will be allowed under this circumstance
Other:	TSH (screening only) FSH (at screening only, to confirm postmenopausal status in non-hysterectomized women with spontaneous amenorrhea for ≥ 6 months but < 12 months and no history of bilateral oophorectomy, and in hysterectomized women who have not undergone bilateral oophorectomy)

Laboratory specimens for hematology, serum chemistry, urinalysis, urine drug screens, and vaginal cytology will be analyzed at certified local laboratories. Bioanalytical samples for PK analysis will be analyzed centrally by Agilex Biolabs.

10.3.1.1.2 Specimen Handling Requirements

Details of specimen handling requirements are provided in the Study Reference Manual.

10.3.1.1.3 Evaluation of Clinical Laboratory Values

The normal ranges of values for the clinical laboratory assessments in this study will be provided by the responsible laboratory and submitted to Daré prior to the beginning of the study. They will be regarded as the reference ranges on which decisions will be made.

If a laboratory value is out of the reference range, it is not necessarily clinically relevant. The investigator must evaluate the out-of-range values and record his or her assessment of the clinical relevance in the appropriate eCRF.

All clinical laboratory values that in the investigator's opinion show clinically relevant or pathological changes during or after termination of treatment must be reported as AEs and followed, as described in Section 11.2.5.

All measurements described in this section are recognized standard methods.

10.3.1.2 Clinical Examinations

10.3.1.2.1 Vital Signs

Vital signs, including pulse rate, respiratory rate, and blood pressure in accordance with the schedule of events (Table 2-1). Assessments will be performed after the participant has been in a supine position for at least 5 minutes. Temperature will also be measured.

Normal ranges for these parameters are as follows:

- Pulse rate: 60 to 100 beats per minute

- Systolic blood pressure: 90 to 140 mmHg
- Diastolic blood pressure: 60 to 90 mmHg
- Respiratory rate: 8 to 22 breaths per minute
- Temperature: 35.5 to 37.5°C

Weight and height will be assessed only assessed at screening.

10.3.1.2.2 Twelve-lead Electrocardiogram

Standard 12-lead ECGs will be performed in accordance with the schedule of events (Table 2-1). All ECGs will be performed after the participant has been supine for at least 5 minutes. All ECG recordings will be identified with the participant number, date, and time of the recording and will be attached to the participant's eCRF.

The ECG should be read by someone with appropriate training to determine that the recording shows a normal sinus rhythm with a rate of 60-100 beats per minute, without evidence of arrhythmias, chamber enlargements, conduction abnormalities, or ischemic heart disease.

10.3.1.2.3 Physical Examination

A complete physical examination (excluding rectal examinations) will be performed at screening and will include a manual breast examination. Subsequent physical examinations, as indicated in the schedule of events (Table 2-1), will be abbreviated and will be directed based on signs and symptoms exhibited by the participant.

Clinically significant abnormal physical examination findings will be reported as an AE (see Section 11.2).

10.3.1.2.4 Vaginal Speculum Examination

Pelvic speculum and visual examinations will be conducted to identify vaginal abnormalities in accordance with the schedule of events (Table 2-1). Clinically significant abnormal findings from the speculum examination will be reported as an AE (see Section 11.2).

In addition, investigators will conduct an assessment of local irritation. Erythema and edema will be rated according to the scores provided in Table 10-1.

In cases of local AEs or local irritation, investigators may take photographs at their own discretion for purposes of sharing visual records with medical monitors.

Table 10-1: Local Irritation Scoring

Reaction Type	0 = None	1 = Mild	2 = Moderate	3 = Severe
Erythema	None	Faint or mild redness of any size OR moderate redness involving ≤ 25% of the area	Moderate redness involving > 25% of the area OR intense redness involving ≤ 25% of the area	Intense redness involving > 25% of the area
Edema	None	Mild visible swelling or barely palpable edema of any size OR easily palpable edema involving ≤ 25% of the area	Moderate visible swelling OR easily palpable edema involving > 25% of the site or gross swelling of firm induration involving ≤ 25% of the area	Gross swelling or firm induration involving > 25% of the area

10.3.1.2.5 Transvaginal Ultrasound

Transvaginal ultrasound will be conducted on women without a history of hysterectomy in accordance with the schedule of events (Table 2-1). The procedure will be conducted in accordance with standard practice at the study site to determine endometrial thickness.

10.3.1.3 Adverse Events

The definitions and management of AEs, and any special considerations for AEs, are provided in Section 11.

10.3.2 Clinical Pharmacology

10.3.2.1 Pharmacokinetic Analysis Methods

The PK characterization of tamoxifen concentrations for each dose to be profiled will use noncompartmental analysis (NCA). Three tamoxifen metabolites (4-hydroxytamoxifen, N-desmethyltamoxifen, and N-desmethyl-4-hydroxytamoxifen [endoxifen]) will also undergo PK characterization.

Standard PK parameters assessed will include measures of the extent of absorption using estimates of the area under the plasma concentration-time curve (AUC), the maximum observed drug concentration (C_{max}), and the time to reach maximum drug concentration (T_{max}). Additional details of the parameters and their calculation and evaluation will be included in the statistical analysis plan (SAP).

10.3.2.1.1 Pharmacokinetic Parameters

The PK parameter estimates will be completed using WinNonlin (Pharsight Corporation). Actual sampling time will be used for all parameter estimation.

Table 10-2 shows the PK parameters that will be computed for each participant for samples obtained over the planned sampling intervals of 24 hours after administration of the IP on Days 1 and 56, with trough samples collected before dosing on Days 4, 7, 10, 18, 28, and 42, and a final sample on Day 63.

Table 10-2: Pharmacokinetic Parameters

Parameter	Description of Parameter
C_{max}	maximum observed drug concentration
T_{max}	time to reach maximum (peak) drug concentration
AUC_{0-t}	area under plasma concentration-time curve from zero to time t
AUC_{0-inf}	area under plasma concentration-time curve from time zero to infinity
$T_{1/2}$	elimination half-life
λ_z	elimination rate constant
V_d	apparent volume of distribution
CL/F	apparent clearance

10.3.2.1.2 Sample Collection

Dense PK sampling will be performed on Day 1 and Day 56, with samples collected immediately before insertion of the IP and at the following time points after insertion:

- 0.5 hours and 1 hour (±10 minutes)
- 2, 4, 5, 8, 12, and 24 hours (±15 minutes)

Trough samples (Days 4, 7, 10, 18, 28, and 42) should be collected within 30 minutes before administration of IP inserts.

A final sample will be collected at the Day 63 follow-up visit.

10.3.3 Pharmacodynamics and Efficacy Variables

10.3.3.1 Vaginal pH

Vaginal swabs for determination of pH will be collected in accordance with the schedule of events (Table 2-1). The pH of vaginal secretions will be measured using pH paper. Additional details and instructions will be provided in the Study Reference Manual.

10.3.3.2 Vaginal Cytology

Samples for vaginal cytology will be collected at the time points specified in the schedule of events (Table 2-1) to determine the maturation index. Investigators should collect a swab of the lateral vaginal wall to be submitted for determination of the vaginal maturation index.

The maturation index is determined by categorizing the ratio of the 3 types of vaginal epithelial cell (parabasal, intermediate, and superficial).

10.3.3.3 Symptoms of Vulvar Vaginal Atrophy

At the Screening Visit, participants will rate the first 4 items in the list of VVA symptoms in Table 10-3 as either not present (none), mild, moderate, or severe, and will indicate whether vaginal bleeding associated with vaginal activity is present or absent. They will then select 1 of the 5 symptoms as their most bothersome symptom. All 5 symptoms will be evaluated again during later study visits (see Table 2-1), and the change in severity from baseline will be determined. Changes from baseline in each participant's most bothersome symptom, as well as changes in dyspareunia (whether dyspareunia was the participant's most bothersome symptom or not), will be evaluated as study endpoints.

Symptoms to be evaluated are shown in Table 10-3.

All participants will be required to engage in vaginal intercourse or other sexual activity (masturbation, etc.) at least 1 time between Days 49-56, and complete an assessment of VVA symptoms in their diary.

Table 10-3: Assessment of Most Bothersome Symptom

Symptom	Assessment
Vaginal dryness	None, mild, moderate, or severe
Vaginal and/or vulvar irritation/itching	None, mild, moderate, or severe
Dysuria	None, mild, moderate, or severe
Vaginal pain associated with sexual activity (dyspareunia)	None, mild, moderate, or severe
Vaginal bleeding associated with sexual activity	Presence versus absence

10.3.3.4 Menopause Quality of Life

The MENQOL™ questionnaire will be given to participants before the first dose and on Day 57, in accordance with the schedule of events (Table 2-1). Developed in 1996, the MENQOL is a self-administered, 29-item questionnaire with 4 domains: vasomotor, physical, psychosocial and sexual. Participants record whether they have experienced the listed problems in the past month, and rate the severity on a Likert scale from 0 (Not at all bothered) to 6 (Extremely bothered).[20,21]

10.3.3.5 Usability and Acceptability Questionnaire

A Usability and Acceptability questionnaire will be administered to all participants in accordance with the schedule of events (Table 2-1).

10.3.3.6 Participant Diaries

Throughout the 56-day administration period, participants will be asked to record their administration of DARE-VVA1 on a paper diary, including the time of placement. Deviations from the planned doses (missed dose or timing) will be recorded on the participant's eCRF.

In addition, participants will be required to engage in vaginal intercourse or other sexual activity (masturbation, etc.) at least 1 time between Days 49 to 56 (see Section 10.3.3.3). Participants will use their diaries to capture their assessment of VVA symptoms.

Study personnel will review diaries at each visit, and diaries will be collected as source documents. Information from participant diaries will be transcribed on the appropriate eCRF pages for documentation of participant compliance with the IP.

10.3.3.7 Pharmacodynamics

Pharmacodynamics will be assessed by correlating the dose administered to dose exposure of tamoxifen in plasma, and then by relating the exposures to local vaginal changes in cytology and pH as well as to the reported symptomatology over 56 days.

11. ADVERSE EVENTS

11.1. Definitions

11.1.1 Adverse Events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Pre-existing diseases or conditions will not be considered AEs unless there is an increase in the frequency or severity, or a change in the quality, of the disease or condition. (Worsening of a pre-existing condition is considered an AE.)

Events that occur in participants treated with control product, or during treatment-free periods of the study, are also considered AEs.

11.1.2 Adverse Drug Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions (ADRs).

The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. All AEs judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to an IP qualify as ADRs.

All AEs for which the judgment of relationship to IP is "possibly related" or higher will be considered ADRs. If a relationship to IP is not provided, then the AE must be treated as if it were "possible."

11.1.3 Unexpected Adverse Event/Adverse Drug Reaction

An expected AE or ADR is one for which the nature or severity is consistent with the applicable scientific information (e.g., IB for an unapproved IP or Product Information document or similar for an approved, marketed product).

An unexpected adverse event (UAE) or unexpected adverse drug reaction (UADR) is one for which the nature or severity is not consistent with the applicable product information (e.g., IB for an unapproved IP or package insert/summary of product characteristics for an approved product). For example, hepatic necrosis would be unexpected (greater severity) if the IB only listed elevated hepatic enzymes or hepatitis. Likewise, cerebral thromboembolism and cerebral vasculitis would be unexpected (greater specificity) if the IB only listed cerebral vascular accidents.

Furthermore, reports that add significant information on specificity or severity of a known, already documented adverse reaction also constitute unexpected events. Examples would be (a) acute renal failure as an expected adverse reaction with a subsequent new occurrence of interstitial nephritis (interstitial nephritis would be unexpected) and (b) hepatitis with a first occurrence of fulminant hepatitis (fulminant hepatitis would be unexpected).

11.1.4 Serious Adverse Events or Serious Drug Reactions

A serious adverse event (SAE) or serious adverse drug reaction (SADR) is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
  NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event/reaction that hypothetically might have caused death if it were more severe.
- requires inpatient hospitalization or prolongation of existing hospitalization
  NOTE: Inpatient hospitalization is defined as 24 hours in a hospital or an overnight stay. An elective hospital admission to treat a condition present before exposure to the IP, or a hospital admission for a diagnostic evaluation of an AE, does not qualify the condition or event as an SAE. Further, an overnight stay in the hospital that is only due to transportation, organization, or accommodation problems and without medical background does not need to be considered an SAE.
- results in persistent or significant disability/incapacity
- is a congenital anomaly
  NOTE: A congenital anomaly in an infant born to a mother who was exposed to the IP during pregnancy is an SAE. However, a newly diagnosed pregnancy in a participant that has received an IP is not considered an SAE unless it is suspected that the IP(s) interacted with a contraceptive method and led to the pregnancy.
- is an important medical event
  NOTE: Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious, such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency, or drug abuse. The occurrence of malignant tumors is also to be considered serious.

11.1.5 Significant Adverse Events

Other significant AEs are defined as marked hematological and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to an intervention, including withdrawal of test drug, dose reduction, or significant additional concomitant therapy.

11.1.6 Treatment-emergent Adverse Events

An AE is defined as treatment emergent if the first onset or worsening is after the first administration of IP (DARE-VVA1 or placebo) and not more than 30 days after the last administration of IP.

11.2. Event Assessment and Follow-up of Adverse Events

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate eCRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. Any AEs characterized as intermittent require documentation of onset and duration of each episode.

The investigator (or designee) will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for nonserious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

11.2.1 Assessment

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE described previously. At each visit, the participant will be allowed time to spontaneously report any issues since the last visit or evaluation. The investigator will then monitor and/or ask about or evaluate AEs using nonleading questions, such as

- "How are you feeling?"
- "Have you experienced any issues since your last visit?"
- "Have you taken any new medications since your last visit?"

Any clinically relevant observations made during the visit will also be considered AEs.

11.2.2 Evaluation

11.2.2.1 Severity of Adverse Events

The clinical severity of an AE will be graded according to the following definitions:

- Grade 1: Mild; the participant experiences awareness of signs or symptoms but these are easily tolerated or managed without specific treatment
- Grade 2: Moderate; the participant experiences discomfort enough to cause interference with usual activity, and/or the condition requires specific treatment

- Grade 3: Severe; the participant is incapacitated with inability to work or do usual activity, and/or the event requires significant treatment measures
- Grade 4: Disabling or with life-threatening consequences, urgent intervention indicated
- Grade 5: Death

It is important to distinguish between severe AEs and SAEs. Severity is a classification of intensity whereas an SAE is an AE that meets serious criteria, as described in Section 11.1.4.

11.2.2.2 Seriousness

The investigator is to evaluate whether the AE meets serious criteria, as described in Section 11.1.4.

11.2.2.3 Actions Taken

Actions taken may consist of:

Dose not changed	An indication that a medication schedule was maintained.
Drug interrupted	An indication that a medication schedule was modified by temporarily terminating a prescribed regimen of medication.
Drug withdrawn	An indication that a medication schedule was modified through termination of a prescribed regimen of medication.
Not applicable	Determination of a value is not relevant in the current context.
Unknown	Not known, not observed, not recorded, or refused.

11.2.2.4 Outcome at the Time of Last Observation

The outcome at the time of last observation will be classified as:

- Recovered/resolved
- Recovered/resolved with sequelae
- Recovering/resolving
- Not recovered/not resolved
- Fatal*
- Unknown

*Investigators should only select fatal as an outcome when the AE results in death. If more than one AE is judged to be possibly related to the participant's death, the outcome of death should be indicated for each such AE. Although "fatal" is usually an event outcome, events such as sudden death or unexplained death should be reported as SAEs.

11.2.2.5 Adverse Event Relationship to Investigational Product

The investigator must make an assessment of each AE's relationship to the IP. The categories for classifying the investigator's opinion of the relationship are as follows:

Not related	The event is most likely produced by other factors such as the participant's clinical condition, intercurrent illness, or concomitant drugs, and does not follow a known response pattern to the study drug, or the temporal relationship of the event to study drug administration makes a causal relationship unlikely
Unlikely related	The event is most likely produced by other factors such as the participant's clinical condition, therapeutic interventions, or concomitant drugs administered to the participant, and it does not follow a known response pattern to the study drug
Possibly related	The event follows a reasonable temporal sequence from the time of drug administration, and/or follows a known response pattern to the study drug, but could have been produced by other factors such as the participant's clinical condition, intercurrent illness, or concomitant drugs
Related	The event follows a reasonable temporal sequence from the time of drug administration, and/or follows a known response pattern to the study drug, and cannot be reasonably explained by other factors such as the participant's clinical condition, intercurrent illness, or concomitant drugs

For SAEs, the event relationship to the IP must be assessed separately by the investigator and Daré.

11.2.3 Documentation

All AEs that occur within the period of observation for the study must be documented in the eCRF with the following information, where appropriate. (The period of observation for the study is described in Section 11.2.)

- AE name or term
- When the AE first occurred (start date and time)
- When the AE stopped (stop date and time or an indication of "ongoing")
- Severity of the AE
- Seriousness (hospitalization, death, etc.)
- Actions taken
- Outcome
- Investigator opinion regarding the AE relationship to the IP

11.2.4 Treatment of Adverse Events

Adverse events that occur during the study will be treated, if necessary, by established standards of care. If such treatment constitutes a deviation from the protocol, the participant may continue

in the study. The decision about whether the participant may continue in the study will be made by the sponsor after consultation with the investigator and/or medical monitor.

If AEs occur in a participant that are not tolerable, the investigator must decide whether to stop the participant's involvement in the study and/or treat the participant. Special procedures may be recommended for the specific IP, such as the collection of a blood sample for determining plasma concentrations of IP, specific tapering procedures, or treatment regimens, as appropriate.

For double-blinded studies, it is not necessary to unblind a participant's treatment assignment in most circumstances, even if an SAE has occurred. If unblinding is necessary, see Section 9.6 for a description of the unblinding procedures.

11.2.5 Follow-up

Any AE will be followed (up to a maximum of 30 days after the last dose of IP) to a satisfactory resolution, until it becomes stable, or until it can be explained by another known cause(s) (i.e., concurrent condition or medication) and clinical judgment indicates that further evaluation is not warranted. All findings relevant to the final outcome of an AE must be reported in the participant's medical record and recorded on the eCRF page.

11.2.6 Reporting

11.2.6.1 Serious Adverse Events

In the event of any SAE reported or observed during the study, whether or not attributable to the study drug, site personnel will report the event to ICON (ICON plc Pharmacovigilance) by email within 24 hours of notification of event in accordance with procedures described in the Study Reference Manual and/or SAE Study Specific Procedure. Site personnel will follow up with a written report to the sponsor on the next working day.

SAE Report Forms will be provided to the clinical research unit to assist in collecting, organizing, and reporting SAEs and follow-up information.

All SAEs should be followed to their resolution, with documentation provided to the sponsor, medical monitor, and ICON on a follow-up SAE Report Form.

At the time of first notification, the investigator or designee should provide the following information, if available:

- Protocol number
- Reporter (study site and investigator)
- Suspect IP
- Participant's study number
- Participant's year of birth
- Participant's gender
- Date of first dose of IP
- Date of last dose of IP, if applicable

- Adverse event term
- Date of occurrence of the event
- A brief description of the event, outcome to date, and any actions taken
- The seriousness criteria(on) that were met
- Concomitant medication at onset of the event
- Relevant medical history information
- Relevant laboratory test findings
- Investigator's opinion of the relationship to IP ("Is there a reasonable possibility that the IP caused the SAE? Yes or No?")
- Whether and when the investigator was unblinded as to the participant's treatment assignment

Any missing or additional relevant follow-up information concerning the SAE should be sent to ICON (ICON plc Pharmacovigilance) as soon as possible with the following minimal information (initial report, adverse event, date of occurrence, participant identification, study number, IP, and site number); this will allow the follow-up information to be linked to the initial SAE report.

Specific information may be requested by ICON plc Pharmacovigilance using a follow-up request form or via email communication.

The investigator is required to comply with applicable regulations (including local laws and guidance) regarding the notification of his or her health authorities, Human Research Ethics Committee (HREC), principal and coordinating investigators, study investigators, and institutions. Each investigator is obligated to learn about the reporting requirements for investigators in his/her country. The study monitor may be able to assist with this.

11.2.6.2 Adverse Drug Reactions

All ADRs should be reported by the investigator in the eCRF.

Suspected serious ADRs must be reported to the sponsor immediately, regardless of the time elapsed since the end of the observation period.

11.2.6.3 Nonserious Adverse Events

Nonserious AEs will be recorded in the eCRF and reported in accordance with the safety management plan.

11.3. Special Considerations

11.3.1 Pregnancy

Not applicable – participants are postmenopausal women. Women of childbearing potential are not eligible for participation.

12. DATA SAFETY MONITORING BOARD

A data safety monitoring board will not be used in this study.

13. STATISTICS

13.1. Statistical Analysis

This section presents a summary of the planned statistical analyses. An SAP that describes the details of the analyses to be conducted will be written prior to database lock.

An analysis of covariance (ANCOVA) model will be used to assess treatment differences in change from baseline for vaginal pH, vaginal cytology, dyspareunia, and most bothersome symptom, using baseline score as a covariate. With no formal testing planned for this study, the *P* values will be informational.

Summary statistics will be provided for the variables described below. For continuous variables, these statistics will typically include the number of participants, mean, standard deviation (SD), median, minimum, and maximum. For categorical variables, these statistics will typically include the number and percentage of participants in each category. The denominator for percentage will be based on the number of participants appropriate for the purpose of analysis.

For all calculations of change from baseline, the last observation recorded before the first administration of the insert (DARE-VVA1 or placebo) will be considered as the baseline observation.

13.1.1 Analysis Populations

The following 3 analysis populations are planned for this study:

- Safety: all participants who are enrolled and receive any amount of planned IP. This population is used for safety analyses.
- Intent-to-treat (ITT): all randomized participants. This population will be used for the analysis of secondary efficacy endpoints.
- PK: all participants who receive at least 1 dose of IP and provide at least 1 quantifiable PK plasma sample. This population will be used for analyses of PK parameters.

All analyses will be performed on non-hysterectomized participants, hysterectomized participants, and all participants taken together. If a participant is randomized incorrectly or is administered the incorrect IP, analyses of the ITT population will be based on the assigned treatment whereas all other analyses will be based on the actual treatment.

13.1.2 Study Participants and Demographics

13.1.2.1 Disposition and Withdrawals

The numbers of participants randomized, completing, and withdrawing, along with reasons for withdrawal, and the number of participants in each analysis population will be tabulated by treatment group and overall.

13.1.2.2 Protocol Deviations

A protocol deviation is defined as any intentional or unintentional change to, or noncompliance with, the approved protocol procedures or requirements. Deviations may result from the action or

inaction of the participant, investigator, or site staff. Examples of deviations include, but are not limited to:

- Failure to adhere to study exclusion and inclusion criteria
- Failure to comply with dispensing or dosing requirements
- Use of medications, food, drink, herbal remedies, or supplements that are specifically prohibited in the protocol
- Missed or out-of-window visits
- Drug dosing not administered within the time frame specified in the protocol
- Failure to adhere to test requirements, including vital signs, laboratory tests, physical examinations, PK blood draws, medical history, etc. – either tests not done, incorrect tests done, or not done within the time frame specified in the protocol
- Procedural deviations such as incorrect storage of IP, failure to update the ICF when new risks become known, failure to obtain HREC approvals for the protocol and ICF revisions

At the outset of the study, a process for defining and handling protocol deviations will be established. This will include determining which violations will be designated "key," requiring immediate notification to the medical monitor and Daré Bioscience Australia Pty LTD. The investigator is responsible for seeing that any known protocol deviations are recorded and handled as agreed.

The number of participants with key/non-key protocol deviations and/or eligibility deviations will be tabulated in categories by treatment group and overall.

13.1.2.3 Demographics and Other Baseline Characteristics

These analyses will be conducted for the Safety and ITT populations.

Demographic variables will include age, height, weight and BMI. Information on race and ethnicity will be collected for any eventual analysis of differences in response to the IP, in accordance with local regulatory requirements. These will be summarized descriptively.

Baseline participant characteristics will include medical history, vaginal speculum examinations, mammograms and CSTs. These will be summarized by treatment group and overall.

13.1.3 Exposure and Compliance

Investigational product administration will be summarized in terms of each participant's total dose, total number of missed doses, duration of exposure, and overall percentage compliance for the IP. Descriptive statistics for these quantities, including the mean, median, SD, minimum, maximum, and quartiles, will be provided by treatment group.

13.1.4 Safety and Tolerability Analyses

Safety analyses will be conducted using data from the safety population (as defined in Section 13.1.1). Descriptive statistics will be calculated for safety data and presented by visit and treatment group for quantitative safety data, and frequency counts will be compiled for classification of qualitative safety data. Safety variables include treatment-emergent adverse

events (TEAEs), clinical laboratory values, vital signs, ECG readings, physical examination results, endometrial thickening in women who have not undergone hysterectomy, and prior and concomitant medications. No formal inferential analyses will be conducted for safety variables, unless otherwise noted.

13.1.4.1 Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 24.0 or higher.

An AE is defined as treatment emergent if the first onset or worsening is after the first administration of IP (DARE-VVA1) and not more than 30 days after the last administration of IP.

The number and percentage of participants with TEAEs will be displayed for each treatment group by system organ class and preferred term. Summaries of TEAEs by severity and relationship to IP will also be provided. All TEAEs leading to IP discontinuation and/or study discontinuation will be summarized separately.

Serious adverse events will be summarized separately in a similar manner by treatment group. Summaries of SAEs by severity and relationship to IP will also be provided. Participant listings of AEs, SAEs, and AEs causing discontinuation of IP will be produced.

13.1.4.2 Clinical Laboratory Evaluations

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual (absolute) values and changes from baseline values will be presented for clinical laboratory values by treatment group at each time point.

The number of participants with clinical laboratory values categorized as below, within, or above normal ranges will be tabulated showing change from baseline (shift tables) for each clinical laboratory analyte by treatment group and by study visit.

Laboratory values that are outside the normal range will also be flagged in the data listings and presented with the corresponding normal ranges. Any out-of-range values that are identified by the investigator as being clinically significant will also be shown in a data listing.

13.1.4.3 Vital Signs

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual values and changes from baseline will be calculated for systolic blood pressure, diastolic blood pressure, heart rate, and respiratory rate, by treatment group.

13.1.4.4 Twelve-lead Electrocardiograms

The number and percentage of participants with normal and abnormal ECG findings will be summarized by treatment group at each time point. Abnormal results will be grouped as clinically significant and not clinically significant.

Descriptive summaries (mean, SD, median, minimum, and maximum) will be presented for ECG measures of PR interval, QRS interval, QT interval, QTc interval (Bazett's and Fridericia's correction methods), and heart rate by treatment group at each time point.

13.1.4.5 Local Site Irritation

Change in local irritation scores (for erythema and edema, see Table 10-1) from baseline to Day 57 will be calculated. Descriptive summaries (mean, SD, median, minimum, and maximum) will be provided for absolute values and for change from baseline by treatment group. In addition, number and percentages of participants with each score will be summarized categorically for erythema and edema separately.

13.1.4.6 Physical Examination Findings

The number and percentage of participants with normal and abnormal findings in the complete physical examination will be displayed by treatment group.

13.1.4.7 Endometrial Thickening

Change in endometrial thickness from baseline in women who have not undergone hysterectomy will be summarized descriptively by treatment group.

13.1.4.8 Prior and Concomitant Medications

Prior medications will be presented separately from concomitant medications. Medications that started before the first dose of IP will be considered prior medications whether or not they were stopped before the first dose of IP. Any medications continuing or starting after the first dose of IP will be considered to be concomitant. If a medication starts before the first dose of IP and continues after the first dose of IP it will be considered both prior and concomitant.

Summary tables by treatment group will be presented by World Health Organization-Anatomical Therapeutic Chemical Classification System (WHO-ATC) therapeutic category and preferred term for participants in the Safety population.

13.1.5 Pharmacokinetics

For noncompartmental analysis, plasma concentrations will be listed and summarized at each time point using descriptive statistics; geometric means and % coefficient of variation (%CV) will also be presented for the PK parameters by treatment group.

Table 10-2 lists the PK parameters that are collected for each participant. The PK parameters will be summarized by dose using descriptive statistics. Calculation of PK parameters will be outlined in the SAP.

For the assessment of dose proportionality, the power model will be implemented for C_{max} and AUC_{0-t}.

13.1.6 Pharmacodynamics and Efficacy Analysis

Efficacy variables will be summarized and analyzed using the ITT population, unless otherwise specified.

13.1.6.1 Primary Analysis

There is no primary efficacy analysis planned for this study.

13.1.6.2 Secondary Analyses

The secondary efficacy endpoints are the following:

- Change of vaginal pH from baseline to Day 57
- Change in vaginal cytology (maturation index; percentage of basal and superficial cells) from baseline to Day 57
- Change in most bothersome symptom from baseline to Day 56
- Change in severity of dyspareunia from baseline to Day 56
- Correlation between exposure and local changes

Descriptive summaries (mean, SD, median, minimum, and maximum) involving change of vaginal pH and vaginal cytology will be presented by treatment group at each time point. In addition, an ANCOVA model will be used to assess treatment differences in change from baseline for vaginal pH, vaginal cytology, dyspareunia, and most bothersome symptom, using baseline score as a covariate. The *P* values will be informational, and no formal testing is planned for this study.

The change in severity from baseline for the most bothersome symptom identified by participants at screening will be summarized categorically by treatment group (see Section 10.3.3.3 for assessment details). In addition, the change in severity from baseline will also be summarized descriptively for each of the 5 symptoms evaluated at each time point.

For assessments of dyspareunia, change in severity from baseline will be summarized descriptively by time point and by treatment group. A categorical summary of severity will be presented by treatment group at each time point.

Pharmacodynamics will be assessed by correlating the dose administered to exposure of tamoxifen in plasma, and then by relating the exposure to local vaginal change in cytology and pH as well as to the reported symptomatology over 56 days. Additional details of this analysis will be provided in the SAP.

13.1.6.3 Exploratory Analyses

Analysis of exploratory endpoints will be conducted in the ITT population.

The exploratory efficacy endpoints are the following:

- Change in the MENQOL questionnaire from baseline to Day 57
- Responses to the Usability and Acceptability questionnaire over time

The MENQOL questionnaire consists of 4 domains and is scored as indicated in the Appendix A. Change from baseline for individual domains and total questionnaire score is summarized descriptively by treatment group and time point.

Details of the analysis of the responses to the Usability and Acceptability questionnaire will be outlined in the SAP.

13.1.7 Interim Analysis

No interim analyses are planned.

13.2. Sample Size Determination

This dose ranging study is not powered for statistical significance. A sample size of 8 participants in each treatment group is considered sufficient to provide information on safety, PK, and PD effects, to guide the design of future studies with DARE-VVA1. A total of 40 participants are planned for this study.

14. STUDY CONDUCT

Steps to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and associated personnel before the study, periodic monitoring visits, and meticulous data management.

14.1. Sponsor and Investigator Responsibilities

14.1.1 Sponsor Responsibilities

The sponsor is obligated to conduct the study in accordance with strict ethical principles (Section 15). The sponsor reserves the right to withdraw a participant from the study (Section 8.3), to terminate participation of a study site at any time (Section 14.7), and/or to discontinue the study (Section 14.6).

Daré agrees to provide the investigator with sufficient material and support to permit the investigator to conduct the study according to the study protocol.

14.1.2 Investigator Responsibilities

By signing the Investigator's Agreement (Section 17.1), the investigator indicates that he or she has read the protocol carefully, fully understands the requirements, and agrees to conduct the study in accordance with the procedures and requirements described in this protocol.

Investigators should ensure that all persons who are delegated study-related responsibilities are adequately qualified and informed about the protocol, the IP, and their specific duties within the context of the study. Investigators are responsible for providing Daré with documentation of the qualifications, Good Clinical Practice (GCP) training, and research experience for themselves and their staff as required by the sponsor and the relevant governing authorities.

To ensure compliance with the guidelines, the study may be audited by an independent person. The investigator agrees, by written consent to this protocol, to cooperate fully with compliance checks by allowing access to all study documentation by authorized individuals.

14.1.3 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the HREC, regulatory agencies, or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including, but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location

for as long a period as dictated by the reviewing HREC, institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to ICON. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by ICON will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

14.2. Site Initiation

Study personnel may not screen or enroll participants into the study until after receiving notification from the sponsor or its designee that the study can be initiated at the study site. The study site will not be authorized for study initiation until:

1. The study site has received the appropriate HREC approval for the protocol and the appropriate ICF.
2. All GCP documents have been submitted to and approved by the sponsor or its designee.
3. The study site has a Clinical Trial Agreement in place.
4. Study site personnel, including the investigator, have participated in a study initiation meeting.

14.3. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the IP or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Participants who fail inclusion and/or exclusion criteria may be rescreened for the study. Participants may only be rescreened once after the original Screening Visit. If a participant is eligible to enter the study after having previously failed screening, the participant will be assigned a new participant identification number.

14.4. Study Documents

14.4.1 Informed Consent

The nature and purpose of the study will be fully explained to each participant (or the participant's legally responsible guardian). The participants must be given ample time and opportunity to inquire about details of the study, to have questions answered to their satisfaction, and to decide whether to participate. Written informed consent must be obtained from each participant (or guardian) prior to any study procedures being performed. A copy of the ICF will be given to the participants for their records.

14.4.2 Good Clinical Practice Documents

The GCP documents are listed below.

- Signed original protocol (i.e., Investigator's Agreement)
- Curricula vitae of all investigators and subinvestigators
- Name and address of the laboratories
- List of laboratory reference ranges, and if available, a quality certificate
- Any other relevant GCP documents

The GCP documents must be received from the investigator and reviewed and approved by Daré or its designee before Daré will authorize shipment of IP to the study site. Copies of the investigator's GCP documents must be retained at the study site in a secure location. Additional documents, including a copy of the protocol and applicable amendment(s), the DARE-VVA1 IB, eCRF completion guidelines, copies of regulatory references, copies of HREC correspondence, and IP accountability records should also be retained as part of the investigator's GCP documents. It is the investigator's responsibility to ensure that copies of all required GCP documents are organized, current, and available for inspection.

A Delegation Log for study-related duties will also be retained at the study site, following signature.

14.4.3 Case Report Forms

By signing the Investigator's Agreement (Section 17.1), the investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories for all participants who sign an ICF.

Case report forms are considered confidential documents and should be handled and stored accordingly. The sponsor or its designee will provide the necessary training on the use of the specific eCRF system used during the study to ensure that the study information is captured accurately and appropriately.

To ensure data accuracy, eCRF data for individual participant visits should be completed as soon as possible after the visit. All requested information must be entered in the electronic data capture (EDC) system according to the completion guidelines provided by the sponsor or its designee.

The eCRFs must be signed by the investigator or a subinvestigator. These signatures serve to attest that the information contained in the eCRF is accurate and true.

14.4.4 Access to Source Data/Documents

The investigator will provide direct access to source data and documents for individuals conducting study-related monitoring, audits, IRB/IEC/HREC review, and regulatory review. The investigator must inform the study participant that his/her study-related records may be reviewed by the above individuals without violating the participant's privacy of personal health information in compliance with Health Insurance Portability and Accountability Act (HIPAA) regulations.

By signing this protocol, the investigator affirms to the sponsor that the investigator will maintain, in confidence, information furnished to him or her by the sponsor and will divulge such

information to the IRB/IEC/HREC under an appropriate understanding of confidentiality with such board.

A paper copy of the laboratory results should be retained with each participant's source data.

14.5. Study Management

14.5.1 Monitoring Procedures

The investigator will permit the site monitor to review study data as frequently as is deemed necessary to ensure data are being recorded in an adequate manner and protocol adherence is satisfactory.

The investigator will provide access to medical records for the monitor to verify eCRF entries. The investigator is expected to cooperate with Daré Bioscience Australia Pty LTD/designee in ensuring the study adheres to GCP requirements.

The investigator may not recruit participants into the study until Daré Bioscience Australia Pty LTD or a designee has conducted a visit at the site to conduct a detailed review of the protocol and eCRF. With agreement of Daré Bioscience Australia Pty LTD, attendance at an investigator meeting may fulfil this requirement.

14.5.2 Data Management

Daré or designee will be responsible for activities associated with the data management of this study. The standard procedures for handling and processing records will be followed per GCP and ICON Clinical Research's standard operating procedures. A comprehensive data management plan (DMP) will be developed, including a data management overview, description of database contents, annotated CRF, pre-entry review list, self-evident correction conventions, query contacts, and consistency checks.

Study site personnel will be responsible for providing resolutions to all data queries. The investigator will be required to document electronic data review to ensure the accuracy of the corrected and/or clarified data. Procedures for soliciting and documenting resolution to data queries are described in the DMP.

14.5.3 Quality Control and Quality Assurance/Audit

Daré Bioscience Australia Pty LTD/ICON will implement and maintain quality control and quality assurance procedures with written standard operating procedures to ensure the study is conducted and data are generated, documented, and reported in compliance with the protocol, GCP, and applicable regulatory requirements.

This study will be subject to audit by Daré or its designee. Audits may be performed to check compliance with GCP guidelines and can include:

- site audits
- Trial Master File audits
- database audits
- document audits (e.g., protocol and/or clinical study report [CSR])

Daré or its designee may conduct additional audits on a selection of study sites, requiring access to participant notes, study documentation, and facilities or laboratories used for the study.

The study site, facilities, all data (including source data), and documentation will be made available for audit by quality assurance auditors and for HREC or regulatory authorities according to GCP guidelines. The investigator agrees to cooperate with the auditor during the visit and will be available to supply the auditor with eCRFs or other files necessary to conduct that audit. Any findings will be strictly confidential.

If a regulatory authority informs the investigator that it intends to conduct an inspection, the investigator shall notify Daré immediately.

Audits may be conducted under either Daré's standard operating procedures or those of an external auditor.

14.6. Study Termination

The study may be terminated at Daré's discretion at any time and for any reason.

14.6.1 Regular Study Termination

The end of this study is defined as the date of the last visit of the last participant (last participant out or last participant last visit) participating in the study. Within 90 days of the end of the clinical study, Daré or designee will notify the HRECs and regulatory authorities about the regular termination of the study as required according to national laws and regulations.

14.6.2 Premature Study Termination

The study may be temporarily suspended or terminated prematurely is there is sufficient reasonable cause at any time by Daré, HRECs, regulatory authorities, respective steering committees, or the coordinating investigator. A decision to prematurely terminate the study is binding to all investigators of all study sites.

Within 15 days of premature termination of a clinical study, Daré or its designee will notify the HRECs and regulatory authorities about the premature termination as required according to national laws and regulations. Daré or its designee must clearly explain the reasons for premature termination.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

If the study is terminated prematurely, all investigators have to inform their participants and take care of appropriate follow-up and further treatment of the participants to ensure protection of the participants' interests. Study sites may be asked to have all participants currently participating in the study complete all of the assessments for the Early Termination Visit.

14.7. Study Site Closure

At the end of the study, all study sites will be closed. Daré may terminate participation of a study site at any time. Examples of conditions that may require premature termination of a study site include, but are not limited to, the following:

- Noncompliance with the protocol and/or applicable regulations and guidelines
- Inadequate participant enrollment

14.7.1 Record Retention

After completing the study, Daré will receive the original CRFs or at least a legible copy and retain the documents for at least 2 years after the completion of the study.

One copy will remain with the investigator. The investigator shall arrange for the retention of the participant identification codes, participant files and other source data until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of the clinical development of the product. These documents need to be retained for a longer period of time if required by applicable regulatory authorities or by agreement with the sponsor.

At the end of such period, the investigator shall notify the sponsor in writing of his or her intent to destroy all such material. The sponsor shall have 30 days to respond to the investigator's notice, and the sponsor shall have a further opportunity to retain such materials at the sponsor's expense.

Copies of these study records (and all study-related documents, including source data) shall be kept by the investigator for the maximum period of time permitted by the hospital, institution, or private practice.

14.7.2 Sample Retention

Samples may be used for purposes related to this research. The samples will be stored until the sponsor has determined that specimens are no longer needed, and the decision has been made that none of the samples needs to be reanalyzed. In addition, identifiable samples can be destroyed at any time at the request of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage may not be possible after the study is completed.

14.8. Changes to the Protocol

Only Daré Bioscience Australia Pty LTD may modify the protocol. Amendments to the protocol will be made only after consultation and agreement between Daré Bioscience Australia Pty LTD, the medical monitor, and the investigator. All amendments that have an impact on participant risk or the study objectives, or require revision of the ICF, must receive approval from the IRB/IEC/HREC prior to their implementation.

14.9. Use of Information and Publication

All information concerning DARE-VVA1, Daré's operations, patent applications, formula, manufacturing processes, basic scientific data, and formulation information supplied by Daré or

its designee to the investigator, and not previously published, is considered confidential and remains the sole property of Daré. Case report forms also remain the property of Daré. The investigator agrees to use this information for purposes of study execution through finalization and will not use it for other purposes without the written consent of the sponsor.

The information developed in this study will be used by Daré in connection with the continued development of DARE-VVA1 and thus may be disclosed as required to other clinical investigators or government regulatory agencies.

Daré Bioscience Australia Pty LTD will retain ownership of all data. All proposed publications based on this study will be subject to Daré Bioscience Australia Pty LTD's approval requirements.

15. ETHICAL AND LEGAL CONSIDERATIONS

15.1. Declaration of Helsinki

This study will be conducted in compliance with the April 1996 ICH Guidance for Industry GCP E6 (including archiving of essential study documents), the Integrated Addendum to ICH E6 (R2) of November 2016, the Declaration of Helsinki, the applicable regulations of the country(ies) in which the study is conducted, and with European Regulation No. 536/2014.

See Appendix B for regulation and guidelines.

15.2. Participant Information and Informed Consent and/or Assent

A properly constituted, valid HREC must review and approve the protocol, the investigator's ICF, and related participant information and recruitment materials before the start of the study.

It is the responsibility of the investigator to ensure that written informed consent is obtained from the participant before any activity or procedure is undertaken that is not part of routine care.

According to the Declaration of Helsinki and ICH GCP, participants must provide their written informed consent prior to enrollment in a clinical study and before any protocol-specified procedures are performed. Participants must declare their consent by personally signing and dating the ICF. The written ICF will embody the elements of informed consent and/or assent as described in the Declaration of Helsinki and will also comply with local regulations.

Each participant should be made aware by the investigator of the nature of the study (objectives, methods, and potential hazards and benefits) and the procedures involved, using the information on the ICF. Information should be given in both oral and written form whenever possible and deemed appropriate by the HREC. Participants, their relatives, or, if necessary, legal representatives must be given ample opportunity to inquire about details of the study.

Participant information and the ICF must be in a language fully comprehensible to the prospective participant. The written information must be provided to the participant to give her sufficient time to understand the information and to prepare questions before being asked for her consent. The investigator must confirm that the text was understood by the participant. The participant will then sign and date the HREC-approved consent form indicating that she has given her consent to participate in the study. The signature confirms that the consent is based on information that has been understood. The form will also be signed by the investigator obtaining the consent and annotated with the study participant number. Each participant's signed ICF must be kept on file by the investigator for possible inspection by regulatory authorities, Daré, and/or the sponsor's designee. Collection of informed consent and/or assent has to be documented on the eCRF.

Furthermore, the participant will be informed that if she wishes to drop out or withdraw (see Section 8.3) at any time during the study, this will not have any negative consequences. Participants may be withdrawn by the investigator if any change related to safety or ethics precludes further participation in the study. Participants will be asked to agree to a final assessment in the event of an early termination of the study.

Participants will be informed that data from their case may be stored in a computer without inclusion of their name and that such data will not be revealed to any unauthorized third party. Data will be reviewed by the monitor, an independent auditor, and possibly by representatives of

regulatory authorities and/or HRECs. The terms of the local data protection legislation will be applied as appropriate.

15.3. Institutional Review Board/Independent Ethics Committee Approval

15.3.1 Ethics Review Prior to Study

The investigator will ensure that the protocol and consent form are reviewed and approved by the appropriate IRB/IEC prior to the start of any study procedures. The IRB/IEC will be appropriately constituted and will perform its functions in accordance with ICH GCP guidelines and local requirements as applicable.

15.3.2 Ethics Review of Other Documents

In addition, the IRB/IEC will approve all protocol amendments (except for Daré Bioscience Australia Pty LTD-approved logistical or administrative changes), written informed consent documents and document updates, Participant recruitment procedures, written information to be provided to the participants, available safety information, information about payment and compensation available to participants, the investigator's curriculum vitae and/or other evidence of qualifications, and any other documents requested by the IRB/IEC and regulatory authority as applicable.

16. REFERENCES

1. Levine KB, Williams RE, Hartmann KE. Vulvovaginal atrophy is strongly associated with female sexual dysfunction among sexually active postmenopausal women. *Menopause.* 2008;15(4 Pt 1):661-666.
2. Nappi RE, Kokot-Kierepa M. Women's voices in the menopause: results from an international survey on vaginal atrophy. *Maturitas.* 2010;67(3):233-238.
3. Santoro N, Komi J. Prevalence and impact of vaginal symptoms among postmenopausal women. *J Sex Med.* 2009;6(8):2133-2142.
4. Faubion SS, Larkin LC, Stuenkel CA, et al. Management of genitourinary syndrome of menopause in women with or at high risk for breast cancer: consensus recommendations from The North American Menopause Society and The International Society for the Study of Women's Sexual Health. *Menopause.* 2018;25(6):596-608.
5. Nappi RE, Kokot-Kierepa M. Vaginal Health: Insights, Views & Attitudes (VIVA) - results from an international survey. *Climacteric.* 2012;15(1):36-44.
6. Boccardo F, Bruzzi P, Rubagotti A, Nicolo GU, Rosso R. Estrogen-like action of tamoxifen on vaginal epithelium in breast cancer patients. *Oncology.* 1981;38(5):281-285.
7. Ferrazzi E, Cartei G, Mattarazzo R, Fiorentino M. Oestrogen-like effect of tamoxifen on vaginal epithelium. *Br Med J.* 1977;1(6072):1351-1352.
8. Friedrich M, Mink D, Villena-Heinsen C, et al. The influence of tamoxifen on the maturation index of vaginal epithelium. *Clin Exp Obstet Gynecol.* 1998;25(4):121-124.
9. Lahti E, Vuopala S, Kauppila A, et al. Maturation of vaginal and endometrial epithelium in postmenopausal breast cancer patients receiving long-term tamoxifen. *Gynecol Oncol.* 1994;55(3 Pt 1):410-414.
10. Love RR, Kurtycz DF, Dumesic DA, Laube DW, Yang Y. The effects of tamoxifen on the vaginal epithelium in postmenopausal women. *J Womens Health Gend Based Med.* 2000;9(5):559-563.
11. Miodrag A, Ekelund P, Burton R, Castleden CM. Tamoxifen and partial oestrogen agonism in postmenopausal women. *Age Ageing.* 1991;20(1):52-54.
12. Shiota A, Igarashi T, Kurose T, Ohno M, Hando T. Reciprocal effects of tamoxifen on hormonal cytology in postmenopausal women. *Acta Cytol.* 2002;46(3):499-506.
13. Vardy MD, Lindsay R, Scotti RJ, et al. Short-term urogenital effects of raloxifene, tamoxifen, and estrogen. *Am J Obstet Gynecol.* 2003;189(1):81-88.
14. Wardell SE, Nelson ER, Mcdonnell DP. From empirical to mechanism-based discovery of clinically useful Selective Estrogen Receptor Modulators (SERMs). *Steroids.* 2014;90:30-38.
15. Chollet J, Mermelstein F, Rocamboli SC, Friend DR. Vaginal tamoxifen for treatment of vulvar and vaginal atrophy: Pharmacokinetics and local tolerance in a rabbit model over 28 days. *Int J Pharm.* 2019;570:118691.
16. Prescribing Information: NOLVADEX (tamoxifen citrate) oral tablets. 2003.
17. Chollet J, Meyn LA, Mermelstein F. Weekly vaginal administration of tamoxifen for three months in postmenopausal women with vulvar and vaginal atrophy: a possible new treatment approach? *Clin Exp Obstet Gynecol.* 2019;46(2):285-288.
18. Prescribing Information: SOLTAMOX (tamoxifen citrate) oral solution. 2018.

19. Parish SJ, Nappi RE, Krychman ML, et al. Impact of vulvovaginal health on postmenopausal women: a review of surveys on symptoms of vulvovaginal atrophy. *Int J Womens Health.* 2013;5:437-447.
20. Hilditch JR, Lewis J, Peter A, et al. A menopause-specific quality of life questionnaire: development and psychometric properties. *Maturitas.* 1996;24(3):161-175.
21. Lewis JE, Hilditch JR, Wong CJ. Further psychometric property development of the Menopause-Specific Quality of Life questionnaire and development of a modified version, MENQOL-Intervention questionnaire. *Maturitas.* 2005;50(3):209-221.

17. ATTACHMENTS

17.1. Investigator's Agreement

PROTOCOL NUMBER:	DARE-VVA-001
PROTOCOL TITLE:	Phase 1/2 Study of Intravaginal Tamoxifen (DARE-VVA1): Randomized, Double-blind, Placebo-controlled Study of Safety, Pharmacokinetics and Pharmacodynamics in Postmenopausal Participants with Moderate to Severe Vulvar and Vaginal Atrophy
AMENDMENT 1 DATE:	Version 2.0, 15-Mar-2022
AMENDMENT 2 DATE:	Version 3.0, 04-Apr-2022

The undersigned acknowledges possession of and has read the DARE-VVA1 IB and has discussed these data with the study monitor. Having considered fully all the available information, the undersigned considers that it is ethically justifiable to give the IP to selected participants in his/her care, according to the study protocol.

He or she agrees to use the study material, including IP, only as specified in the protocol. He or she understands that changes cannot be made to the protocol without prior written approval of Daré Bioscience Inc.

He or she understands that any deviation from the protocol may lead to early termination of the study.

He or she agrees to report to Daré Bioscience Inc within the specified timeframe any clinical AE or abnormal laboratory value that is serious, whether or not considered related to the administration of IP.

He or she agrees to comply with Daré Bioscience Inc and regulatory requirements for the monitoring and auditing of this study.

In addition, he or she agrees that the study will be carried out in accordance ICH, the Declaration of Helsinki, and the local laws and regulations relevant to the use of new therapeutic agents.

I, the undersigned, have carefully read this protocol and agree that it contains all the necessary information required to conduct the study.

Principal Investigator:
Printed Name:

Signature:

Date:

Investigator's name and address (stamp)

APPENDICES

A. Study-specific Requirements

Symptoms of Vulvar Vaginal Atrophy

Study participants will be enrolled who have no greater than 5 percent superficial cells on a vaginal smear, have a vaginal pH > 5.0, and have either self-identified at least 1 of the first 4 symptoms in the list below as being moderate to severe, or that vaginal bleeding associated with sexual activity is present.

Patient self-assessed symptoms of vulvar and vaginal atrophy include:

- Vaginal dryness (none, mild, moderate, or severe)
- Vaginal and/or vulvar irritation/itching (none, mild, moderate, or severe)
- Dysuria (none, mild, moderate, or severe)
- Vaginal pain associated with sexual activity (dyspareunia) (none, mild, moderate, or severe)
- Vaginal bleeding associated with sexual activity (presence vs. absence)

Local Site Irritation

Pelvic speculum and visual examinations will be conducted to identify vaginal abnormalities. As part of this assessment, investigators will conduct an assessment of local irritation in terms of erythema and edema, as shown below.

Reaction Type	**0 = None**	**1 = Mild**	**2 = Moderate**	**3 = Severe**
Erythema	None	Faint or mild redness of any size OR moderate redness involving ≤ 25% of the area	Moderate redness involving > 25% of the area OR intense redness involving ≤ 25% of the area	Intense redness involving > 25% of the area
Edema	None	Mild visible swelling or barely palpable edema of any size OR easily palpable edema involving ≤ 25% of the area	Moderate visible swelling OR easily palpable edema involving > 25% of the site or gross swelling of firm induration involving ≤ 25% of the area	Gross swelling or firm induration involving > 25% of the area

Menopause Quality of Life: MENQOL

Developed in 1996, the MENQOL is a self-administered, 29-item questionnaire with 4 domains: vasomotor, physical, psychosocial and sexual. Participants record whether they have experienced the listed problems in the past month and rate the severity on a Likert scale from 0 (Not at all bothered) to 6 (Extremely bothered).

The MENQOL instrument is provided here.

Study Specifics:

Subject ID # :_____ **Date :**_____ /_____ /_____
yy mm dd

THE MENOPAUSE-SPECIFIC

QUALITY-OF-LIFE QUESTIONNAIRE

MENQOL™

Primary Care Research Unit
Department of Family and Community Medicine
Sunnybrook Health Sciences Centre
University of Toronto

Authors: John R. Hilditch, Jacqueline E. Lewis, Peter G. Norton, Earl V. Dunn

The development of the MENQOL™ questionnaire was funded by CIBA-GEIGY Canada Ltd., Mississauga, Canada

The authors request citation of the 1996 and 2005 development papers whenever MENQOL or MENQOL-I is used or otherwise acknowledged.

For information or permission to use the questionnaire, please submit a request through ePROVIDE™, Mapi Research Trust, online platform.

MENQOL™ (1 month recall)
MENQOL - Canada/English - Mapi.
ID0295-TR-72179 / MENQOL_AU2.2_1month-recall_eng-CAorl.doc

INSTRUCTIONS

Each of the items in the questionnaire is in the form of the examples below:

		Not at all bothered → Extremely bothered 0 1 2 3 4 5 6
NIGHT SWEATS	☐ No	☐ Yes → ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6

Indicate whether or not you have experienced this problem in the **PAST MONTH**.

IF YOU ***HAVE NOT*** EXPERIENCED THE PROBLEM:

Mark "No"

NIGHT SWEATS	☑ No	☐ Yes → ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6

→ Go to the next item.

IF YOU ***HAVE*** EXPERIENCED THE PROBLEM:

Mark "Yes", then check off how bothered you were by the problem.

NIGHT SWEATS	☐ No	☑ Yes → ☐ 0 ☐ 1 ☑ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6

→ Go to the next item.

This questionnaire is completely confidential. Your name will not be associated with your responses. However, if for any reason you do not wish to complete an item, please leave it and go on to the next one.

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The Menopause-Specific Quality of Life Questionnaire *Page 3 of 4*

Date :_____/ _____/ _____ Subject ID # :_____
yy mm dd

For each of the following items, indicate whether you have experienced the problem in the **PAST MONTH**. If you have, rate how much you have been ***bothered*** by the problem.

			Not at all bothered → Extremely bothered						
			0	1	2	3	4	5	6
1. HOT FLUSHES OR FLASHES	☐ No	☐ Yes →	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
2. NIGHT SWEATS	☐ No	☐ Yes →	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
3. SWEATING	☐ No	☐ Yes →	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
4. DISSATISFACTION WITH MY PERSONAL LIFE	☐ No	☐ Yes →	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
5. FEELING ANXIOUS OR NERVOUS	☐ No	☐ Yes →	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
6. POOR MEMORY	☐ No	☐ Yes →	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
7. ACCOMPLISHING LESS THAN I USED TO	☐ No	☐ Yes →	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
8. FEELING DEPRESSED, DOWN OR BLUE	☐ No	☐ Yes →	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
9. BEING IMPATIENT WITH OTHER PEOPLE	☐ No	☐ Yes →	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
10. FEELINGS OF WANTING TO BE ALONE	☐ No	☐ Yes →	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
11. FLATULENCE (WIND) OR GAS PAINS	☐ No	☐ Yes →	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
12. ACHING IN MUSCLES AND JOINTS	☐ No	☐ Yes →	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
13. FEELING TIRED OR WORN OUT	☐ No	☐ Yes →	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
14. DIFFICULTY SLEEPING	☐ No	☐ Yes →	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
15. ACHES IN BACK OF NECK OR HEAD	☐ No	☐ Yes →	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
16. DECREASE IN PHYSICAL STRENGTH	☐ No	☐ Yes →	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

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The Menopause-Specific Quality of Life Questionnaire *Page 4 of 4*

Date : _____/ _____/ _____ Subject ID # : _____
yy mm dd

			Not at all bothered → Extremely bothered						
			0	1	2	3	4	5	6
17. DECREASE IN STAMINA	☐ No	☐ Yes →	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
18. LACK OF ENERGY	☐ No	☐ Yes →	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
19. DRY SKIN	☐ No	☐ Yes →	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
20. WEIGHT GAIN	☐ No	☐ Yes →	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
21. INCREASED FACIAL HAIR	☐ No	☐ Yes →	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
22. CHANGES IN APPEARANCE, TEXTURE OR TONE OF MY SKIN	☐ No	☐ Yes →	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
23. FEELING BLOATED	☐ No	☐ Yes →	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
24. LOW BACKACHE	☐ No	☐ Yes →	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
25. FREQUENT URINATION	☐ No	☐ Yes →	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
26. INVOLUNTARY URINATION WHEN LAUGHING OR COUGHING	☐ No	☐ Yes →	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
27. DECREASE IN MY SEXUAL DESIRE	☐ No	☐ Yes →	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
28. VAGINAL DRYNESS	☐ No	☐ Yes →	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
29. AVOIDING INTIMACY	☐ No	☐ Yes →	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

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MENQOL - Canada/English - Mapi.
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INSTRUCTIONS FOR USE AND SCORING OF THE MENOPAUSE-SPECIFIC QUALITY OF LIFE QUESTIONNAIRE MENQOL™

USE:

1. The title page, subject questionnaire instruction and 29 items constitute the official MENQOL™.
2. Pages i, ii, and iii inclusive contain information for the researchers only.
3. Ensure you have the correct questionnaire recall period based upon your study need.
4. The MENQOL™ questionnaire is designed to be self-administered either in person or by mail.
5. Use of electronic, verbal, Braille, sign language or other delivery methods require pre-testing.
6. Researchers are advised to pre-test the average time required by subjects to complete the questionnaire.

REFERENCES :

Hilditch JR, Lewis J, Peter A, van Maris B, Ross A, Franssen E, Guyatt GH, Norton PG, Dunn E. A Menopause-Specific Quality of Life Questionnaire: development and psychometric properties. Maturitas 1996;24: 161-75

Lewis JE, Hilditch JR, Wong CJ. Further psychometric property development of the Menopause-Specific Quality of Life questionnaire and development of a modified version, the MENQOL-Intervention questionnaire. Maturitas 2005; 50:209-221.

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SCORING:

1. Convert the Subject Response (the item raw data score) to a Conversion Score (a score for further analyses), in the following manner:

Subject Response	Conversion Score
No	1
Yes 0	2
1	3
2	4
3	5
4	6
5	7
6	8

2. a) The MENQOL™ contains four domains.
   - i Vasomotor - Items 1 to 3
   - ii Psychosocial - Items 4 to 10
   - iii Physical - Items 11 to 26
   - iv Sexual - Items 27 to 29

   b) Each domain is scored separately.

   c) After conversion, each domain mean ranges from 1 to 8.

3. The overall questionnaire score is the mean of the domain means.

4. Interpretation of results:
   a) The questionnaire instructions ask the subject to check the "No" box if she does not experience the item. The Conversion Score, '1', means the individual does not experience the item.

   b) The Subject Response, "Yes" with a raw data score '0', has an important meaning in the MENQOL™ because it permits the subject to experience the item, "Yes", BUT to be "Not at all bothered" by the item's occurrence. The Conversion Score '2' means the subject experiences the item BUT is "Not at all bothered" by the experience.

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c) Conversion score '3' means the subject experiences the item, "Yes" and is minimally bothered, raw score '1'.
Conversion score '4' is the equivalent of a bothersome raw score of '2'.
Conversion score '5' is the equivalent of a bothersome raw score of '3'.
Conversion score '6' is the equivalent of a bothersome raw score of '4'.
Conversion score '7' is the equivalent of a bothersome raw score of '5'.
Conversion score '8' means the subject experiences the item and is 'Extremely bothered', reflecting a raw data score of '6'.

d) Hence, the Conversion score ranges from 1 to 8; whereas, the questionnaire raw data score is NO or Yes, with a bothersome score of '0' "Not at all bothered" worsening to '6', "Extremely bothered".

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B. Regulations and Good Clinical Practice Guidelines

1. Regulations

Refer to the following Australian regulations:

- Therapeutic Goods Act 1989
- Therapeutic Goods Regulations 1990

2. Good Clinical Practice Guidelines

ICH GCP guidelines can be found at the following URLs:

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4.pdf